



# Endocrinology

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# Endocrinology

## *The Bulletin of the Association for the Study of Internal Secretions*

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### OSSEOUS DEVELOPMENT IN ENDOCRINE DISORDERS\*

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The striking variations of stature in the eunuch, the acromegalic, and the various types of infantilism have been of historical interest even to the layman. An illustration of this interest is the prize offered by the philanthropist for the intermarriage of giants in order to produce a larger and stronger race. These outspoken differences in size and local osseous proportions of the individual were among the first signs giving impetus to the scientist to study the hormonie effects of the internal secretions upon skeleton growth. C. v. Langer (1872) was probably the first to distinguish between pathological and normal giants. To Pierre Marie (1888-89), Massalongo (1892), Sternberg (1895), Brissaud and Meige (1895), and Launois and Roy (1902-04) credit should be given for the earliest work relating the development of the osseous system in gigantism and acromegaly to the hypophysis. Tandler and Grosz (1907-10) in their studies of the skopzen directly associated the overgrowth of the long bones present in the early hypogonad states to castration.

These early investigations, besides indicating a general change in the osseous system present in various ductless gland disorders, were pointing the way to local osseous abnormalities

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\*Address of President of Association for the Study of Internal Secretions, San Francisco, June 23, 1923.

in the growth and development of individual bones as related to special glandular function. Soon after the discovery of the x-ray, roentgenology was applied with more minutiae to determine in the living the development of the osseous nuclei and the closure of the epiphyseal ends, which clinical deduction had predicted would vary in the endocrine subjects from those of the normal. Hertoghe (1896), v. Wyss (1899-1900), Kasowitz (1902), Diederle (1906), Siegert (1910), and others were the first to demonstrate by this means the presence of retarded carpal development in juvenile hypothyroidism.

In a clinical material of over 2,000 endocrine observations,† the striking differences in the osseous development, general and local, led the writers to suspect that there might be some specific predilection of the various hormones of special ductless glands in their effect upon the growth and development of the individual types of bones; i. e., short, flat, or long bones. This led to the following studies, which were undertaken to determine: (1) the normal osseous development in the various ages from one month to twenty-five, during the skeletal growth; (2) the variations from this normal development in the various endocrine disorders, such as hypothyroidism, pituitarism, gonadism, pinealism, thymolymphatic hypoplasia, pluriglandularism, etc.; and (3) the possible specific character of the internal secretions of these various glands in their effect upon the individual growth of one set of bones, such as the flat, long, or short. If such specific osseous hormone effects are presented, or even if definite general osseous changes, recognizable by roentgenograms, do occur in some of these endocrine disorders, they would be of great value in the early diagnosis of the disorders of the glands, as well as a specific measure of their function and the treatment effects of these dyscrasias. These studies apply only to the age of twenty-five, at which time the osseous development is normally completed.

In order to draw any convincing conclusions from these comparisons, it was first necessary to determine a normal for each age and then to agree upon the definition of a grouping of the various endocrine disorders, both of which precepts are very difficult and probably can not be established beyond criticism. Before accepting individuals as normals for the various ages, they were carefully examined clinically and roentgenologically.

†Clinical observations of this material were made with Dr. J. L. Tierney.

Chart I  
 UPPER EXTREMITY (GRAY'S ANATOMY)

BONES	APPEARANCE OF OSSIFICATION CENTERS	UNION
Humerus 8 centers	Shaft: 5th wk. fetal life. Head: 1st yr. Greater tubercle: 3rd yr. Lesser tubercle: 5th yr. Capitellum: End of 2nd yr. Medial epicondyle: 5th yr. Lateral epicondyle: 13th to 14th yr.	Head and tubercles: 6th yr. Upper epiphysis with body: 20th yr. Lower epiphysis with body: 18th yr.
Ulna 3 centers	Body: 8th wk. fetal life. Head (inferior extremity): 4th yr. Olecranon: 10th yr.	Upper epiphysis: 16th yr. Lower epiphysis: 20th yr.
Radius 3 centers	Body: 8th wk. fetal life. Lower epiphysis: 2nd yr. Upper epiphysis: 5th yr.	Upper epiphysis: 17th to 18th yr. Lower epiphysis: 20th yr.
Carpal bones 1 center for each	Capitate: 1st yr. Hamate: 1st yr. Triangular: 3rd yr. Lunate: 6th yr. Greater multangular: 5th yr. Navicular: 6th yr. Lesser multangular: 8th yr. Pisiform: 12th yr.	
Metacarpals 2 centers	Body: 8th wk. fetal life. Distal extremity: 3rd yr. Base of thumb metacarpal: 3rd yr.	20th yr.
Phalanges 2 centers	Body: 8th wk. fetal life. Proximal extremity:- 1. First row: 3rd to 4th yr. 2. Second and third rows: 4th to 5th yr.	18th to 20th yr.

Chart II  
LOWER EXTREMITY (GRAY'S ANATOMY)

BONES	APPEARANCE OF OSSIFICATION CENTERS	UNION
<b>Os coxae</b> 8 centers	Primary:- 1. Ilium: 8th wk. fetal life. 2. Ischium: 3rd mo. 3. Pubis: 5th mo. Secondary:- 1. Crest of ilium ) 2. Antero-inferior spine ) 3. Tuberosity of ischium ) - puberty. 4. Pubic symphysis ) 5. Acetabulum )	Ilium ) Ischium ) 18th yr. Pubis )  Secondary and primary centers: 20th to 25th yr.
<b>Femur</b> 5 centers	Body: 7th wk. fetal life. Head: End of 1st yr. Greater trochanter: 4th yr. Lesser trochanter: 13th to 14th yr. Lower epiphysis: 9th mo. fetal life. 2nd to 3rd yr. Complete at puberty.	All united after puberty in reverse order of their ap- pearance. Lower epiphysis at 20th yr.
<b>Patella</b> 1 center		
<b>Tibia</b> 3 centers	Body: 7th wk. fetal life. Upper epiphysis: 2nd yr. Lower epiphysis: 2nd yr.	Lower with body: 18th yr. Upper with body: 20th yr.
<b>Fibula</b> 3 centers	Body: 8th wk. fetal life. Lower epiphysis: 2nd yr. Upper epiphysis: 4th yr.	Lower with body: 20th yr. Upper with body: 25th yr.
<b>Tarsus</b> 7 centers	Calcaneus: 8th mo. fetal life. Talus: 7th mo. fetal life. Cuboid: 9th mo. fetal life. 3rd cuneiform: 1st yr. 1st cuneiform: 3rd yr. 2nd cuneiform and navicular: 4th yr.	
<b>Metatarsals</b> 2 centers	Body: 9th wk. fetal life. Base of first metatarsal: 3rd yr. Heads of second, third, fourth, and fifth: 5th to 8th yr.	18th to 20th yr.
<b>Phalanges</b> 2 centers	Body: 10th wk. fetal life. Base: 4th to 10th yr.	18th yr.

The clinical examination consisted of investigating the family history, particularly for endocrine and hereditary conditions, including blood examinations of the parents. A complete medical survey of each individual, including comparison for the height, weight and age with the normal (established by tables of Browning, Bowditch and Holt for infants and children and insurance tables for adults) was then made. Provided the individual was considered normal according to these qualifications (i. e., family history, personal history, physical examination, and standard tables) he was then x-rayed and the roentgenological findings were compared with those for the various ages as given by Gray's Anatomy and the radiological studies of Baetjer and Waters, Knox, and Rotch. Decided variations, with personal exceptions enumerated in the following charts, in the roentgenological determinations of the osseous system from those already considered within the normal by these four authorities were excluded as possible normals. Normals were examined eight to ten days after birth, at six months, one year, eighteen months, two years, and for each year up to the age of twenty-five. A number of each age were examined until enough were found without physical or roentgenological variations from the normal to establish a standard. This work presented a great many difficulties and required a long time in order to exclude the abnormals physically and then finally to determine the roentgenological normal. The four authorities quoted above giving normals for the various ages differed considerably in their opinions upon certain osseous developments as displayed by the roentgenogram, as shown by Charts I to VII.

In order to obtain some estimation of the roentgenological findings of the various ages, the individual bones of the body were first classified from an anatomical viewpoint, as given by Gray's Anatomy, Charts I and II, on pages 3 and 4.

The bones according to the appearance of centers of ossification and union of the epiphyses for the yearly ages were then *arranged by years* according to Gray's Anatomy (Chart III).

The appearance and union of the centers of various bones of the body were then compared, according to Gray's Anatomy and the roentgenographic studies of Baetjer and Waters and of Knox (Charts IV and V).



Chart IV  
APPEARANCE AND UNION OF BONE CENTERS, UPPER EXTREMITY, ACCORDING TO

BONES	GRAY'S ANATOMY		BARTJER AND WATERS		KNOX	
	APPEAR	UNITE	APPEAR	UNITE	APPEAR	UNITE
Scapula	15th-16th	25th	15th	18th	15th-17th	22nd-25th
1.Acromion (2 cent.)	1st-17th	"	1st	18th	1st and	15th
2.Coracoid (" " )	16th	"	15th	18th	15th-17th	22nd-25th
3.Inferior angle	18th-20th	25th	15th-17th	23rd-25th	18th-20th	25th
Clavicle	1st	Head & tubercles, 6th.	6th-7th mo.	6th	1st	5th
1.Sternal end	3rd	Head & shaft, 20th.	3rd-4th yr.	"	3rd	"
Humerus	5th		"	"	5th	"
2.Greater tubercle	2nd	4, 5, 6 & 7: Unite with shaft at 18th yr.	1st	18th-19th	2nd	Head and shaft, 20th.
3.Lesser	5th		5th	"	5th	"
4.Capitellum	12th		10th-11th	"	12th	"
5.Medial epicondyle	13th-14th		12th-14th	"	13th-14th	"
6.Trochlea	4th	20th	4th	18th	4th	20th
7.Lateral epicondyle	10th	16th	8th-9th	17th	10th	16th
Ulna	2nd	20th	2nd	16th-17th	2nd	20th
1.Lower epiphysis	5th	17th-18th	5th	16th-17th	5th	17th-18th
Radius	1st		1, 2, 3, 4, 5, 6 & 7: Appear in anatomical order, one bone for each year.		1, 2, 3, 4, 5, 6, 7 & 8: Appear in anatomical order.	
1.Hamate (unciform)	"					
2.Triang. (cuneiform)	3rd					
3.Lunate (semilunar)	5th					
4.Scap. mult. (trapezium)	6th					
5.Navicular (scaphoid)	8th					
6.Trapez. (trapezoid)	8th					
7.Less. mult. (trapezoid)	12th					
8.Pisiform (pisiform)	12th					
Metacarpals	3rd	20th	3rd	17th-18th	3rd	18th
1.Digital extremity	"	"	"	"	"	"
2.Base of 1st	3rd-4th	18th-20th	3rd	16th-17th	3rd-4th	18th-20th
Phalanges	4th-5th	"	"	"	4th-5th	"
1.Head, 1st row						
2. " 2nd and 3rd rows						

Chart V  
APPEARANCE AND UNION OF BONE CENTERS, LOWER EXTREMITY, ACCORDING TO  
THAY'S ANATOMY

BONES	APPEAR	WHITE	APPEAR	WHITE	APPEAR	WHITE	KNOW
Os Coxae							
1. Prim. centers	Birth	18th	Birth	16th-16th	Birth	18th	
a. Ilium	"	"	"	"	"	"	
b. Ischium	"	"	"	"	"	"	
c. Pubis	"	"	"	"	"	"	P & I, 7th-8th
2. Sec. centers	Puberty	20th-26th	15th	20th	Puberty	26th	
a. Ant.-inf. sp.	"	"	"	"	"	"	
b. Pub. ischium	"	"	"	"	"	"	
c. Pubic symph.	"	"	"	"	"	"	
d. Crest ilium	"	"	16th-18th	23rd-28th	"	"	
e. Acetabulum	"	"	15th-16th	16th-16th	"	"	
Femur	End of 1st	1, 2 and 3; Reverse order	End of 1st	17th-18th	End of 1st	1, 2 and 3; Reverse order	
1. Head	4th	of appearance, 4th	18th	17th	4th	of appearance, 4th	
2. Greater troch.	13th-14th	after puberty.	11th-13th	17th	13th-14th	after puberty.	
3. Lesser "	9th mo.fet.	4. 20th	Birth	18th-20th	9th mo.fet.	4. 20th	
4. Lower epiph.	life				life		
Patella	2nd-3rd		3rd-4th		3rd		
Tibia	2nd	20th	1st	10th-20th	Birth	20th	
1. Upper epiph.	"	18th	2nd	17th-18th	2nd	18th	
2. Lower							
Fibula	4th	25th	3rd-4th	17th-18th	4th	25th	
1. Upper epiph.	2nd	20th	2nd	17th-18th	2nd	20th	
2. Lower							
Tarsus	6th mo.fet.	Cent. for epi-physia os cal-physia os cal-	Def. birth	Cent. for epi-physia os cal-	6th mo.fet.	Cent. for epi-physia os cal-	
1. Calcaneus (os calcis)	life	physia os cal-	"	physia os cal-	life	physia os cal-	
2. Talus (astrag- alus)	7th mo.fet.	cia appears at 10th yr. and unites after puberty.	"	cia appears at 10th yr. and unites at 18th.	7th mo.fet.	cia appears at 10th yr. and unites after puberty.	
3. Cuboid (os cub- oidum)	8th mo.fet.	life	"	end unites at 18th.	8th mo.fet.	and unites after puberty.	
4. 3rd cuneiform	1st		1st		1st		
5. 1st (external)	3rd		3rd		3rd		
6. 2nd (middle)	4th		4th		4th		
7. Navicular (scaphoid)							
Metatarsals	3rd	18th-20th	3rd-7th	About 17th	3rd	18th-20th	
1. Base of 1st	5th-8th						
2. Heads of 2nd to 5th							
Phalanges	4th-10th	18th	3rd-7th	17th	Not given		
1. Bases							

No. 1 GRAY'S ANATOMY APPEARANCE AND UNION OF BONE CENTERS BY YEARS, ACCORDING TO Chart VI			
	BAETJER AND WATERS	KNOX	ROTCH
1	Coracoid proc. scapula Head humerus Capitate & hamate Head femur (birth) 3rd cuneiform	Coracoid proc. scapula Head humerus Capitate & hamate Head femur Upp. epiph. tibia 3rd cuneiform	Head humerus (6-8 mos.) Capitellum, humerus (2-3) Capitate & hamate Head femur Upp. epiph. tibia (birth)
2	Capitellum, humerus Low. epiph. radius Patella (2-3) Upp. epiph. tibia Low. epiph. tibia Low. epiph. fibula	Capitellum, humerus Low. epiph. radius Low. epiph. tibia Low. epiph. fibula	Low. epiph. radius (2-4) Patella (2-3) Low. epiph. tibia (12th mo.-2nd yr.) Low. epiph. fibula (2-5)
3	Gr. tuberos. humerus Os triangul. aris Hoods metacarpals Hoods prox. phalang. (3-4) 1st cuneiform Hoods metatarsals (3-8)	Gr. tuberos. humerus Os triangul. aris Hoods metacarpals Hoods prox. phalang. (3-4) Patella 1st cuneiform Hoods metatarsals (3-7) Low. epiph. ulna Gr. troch. femur Upp. epiph. fibula (3-4) Navicular (tarsal)	Tubercosities humerus (2-3) Os triangul. aris (2-3) Hoods metacarpals Hoods phalanges (3-4) 1st cuneiform Hoods metatars. (3-8) Styloid proc. ulna Lunate (4-8) Upp. epiph. fibula 2nd cuneiform Navicular (tarsal) Hoods phalang. (feet) (4-8)
4	Low. epiph. ulna Hoods phalanges, 2nd & 3rd rows Gr. troch. femur Upp. epiph. fibula 2nd cuneiform Navicular (tarsal)	Low. epiph. ulna Gr. troch. femur Upp. epiph. fibula 2nd cuneiform Navicular (tarsal) Med. epicond. humerus Upp. epiph. radius Lunate & gr. multang.	Med. epicond. humerus U. head & tub. humerus Upp. epiph. radius Low. epiph. ulna (6-7) Gr. multangular Navic. (carpal) (5-6) Gr. troch. femur Less. multang. (6-8) Union is ch. & pub. (8-8)
5	Union head & tuber- cles humerus Navicular (carpal)	Union head & tuber- cles humerus Lunate & gr. multang. Navicular (carpal)	Less. multang. (6-8) Union is ch. & pub. (8-8)
6	Union isch. & pub. (7-8)	Less. multang. (7th?) Union isch. & pub. (7-9)	Less. multang. (7th?) Union isch. & pub. (7-8)
7	Union isch. & pub. (7-8)	Less. multang. (7th?) Union isch. & pub. (7-9)	Less. multang. (7th?) Union isch. & pub. (7-8)
8	Less. multangular	Pisiform (8-11) Ulna (8-9)	Pisiform (8-11) Ulna (8-9)
9	Ulna	Ulna	Ulna
10	Olecranon, ulna Epiph. os calcis	Ulna Epiph. os calcis	Epiph. os calcis (9th) Olecranon, ulna Epiph. os calcis
11	Less. troch. femur (11-12)	Less. troch. femur (11-13)	Less. troch. femur (11-13)
12	Pisiform	Pisiform	Pisiform

Less. troch. femur (12-14)

No. 2 Chart VII APPEARANCE AND UNION OF BONE CENTERS BY YEARS, ACCORDING TO GRAVE'S ANATOMY BARTER AND WATERS			
Yrs	GRAVE'S ANATOMY (15-18)	BARTER AND WATERS	KNOX (15-18)
15	Lat. epicond. humerus (15-18)		Lat. epicond. humerus (15-18)
16	A. of scromion (15-18) U. of scromion (15-18) Sec. centers of coxae U. of epiph. os calcis	A. of scromion U. of angle scapula Int. angle scapula (15-18) Sec. centers of coxae Sternal end clav. (15-18) A. of sec. centers of coxae a. Crest ilium (15-18) b. Acetabulum (15-18) U. of prim. centers of coxae Union of:- Upp. epiph. radius (16-17) Hads phalang. hand (16-17)	Lat. epicond. humerus (15-18) Less. troch. femur (15-18) U. of scromion (16-17) Int. angle scapula Sec. centers of coxae U. of epiph. os calcis
17	A. of inf. angle scapula U. of olecranon	Union of:- Upp. epiph. radius (16-17) Hads phalang. hand (16-17)	Union of:- Dist. extr. humer. (16-18) Olecranon
18	U. of inf. angle scapula U. of olecranon	Union of:- Upp. epiph. radius (17-18) Less. troch. femur	Union of:- Dist. extr. humer. (17-18) Less. troch. femur Upp. epiph. radius (17-18)
19	A. of sternal end clav- icle (18-20) Union of:- Dist. extr. humerus Hads phalang. hand (18-20) Prim. centers of coxae Head femur Gr. troch. femur Low. epiph. tibia Upp. epiph. tibia (18-20) Hads phalang. foot	Union of:- Dist. extr. humerus (17-18) Hads metacarpals (17-18) Head femur (17-18) Less. troch. femur Low. epiph. tibia (17-18) Upp. epiph. tibia (17-18) Hads metatars. (about 17) Hads phalanges foot (about 17) Union of:- Dist. extr. humerus (18-19) Low. epiph. ulna Gr. troch. femur Low. epiph. femur (18-20) Upp. epiph. tibia (18-20) Upp. epiph. fibula (18-20)	A. of sternal end clav- icle (18-20) Union of:- Hads metacarpals Hads phalang. hand (18-20) Prim. centers of coxae Head femur Gr. troch. femur Low. epiph. tibia Hads metatars. (18-20)
20	U. of inf. angle scapula U. of olecranon	Union of:- Upp. epiph. radius (18-20) Less. troch. femur Upp. epiph. radius (18-20) Hads phalang. foot	Union of:- Dist. extr. humer. (18-20) Less. troch. femur Upp. epiph. radius (18-20) Hads phalang. foot
21	A. of sternal end clav- icle (18-20) Union of:- Dist. extr. humerus Hads phalang. hand (18-20) Prim. centers of coxae Head femur Gr. troch. femur Low. epiph. tibia Upp. epiph. tibia (18-20) Upp. epiph. fibula (18-20)	Union of:- Dist. extr. humerus (18-19) Low. epiph. ulna Gr. troch. femur Low. epiph. femur (18-20) Upp. epiph. tibia (18-20) Upp. epiph. fibula (18-20)	A. of sternal end clav- icle (18-20) Union of:- Hads metacarpals Hads phalang. hand (18-20) Prim. centers of coxae Head femur Gr. troch. femur Low. epiph. tibia Hads metatars. (18-20)
22	U. of inf. angle scapula U. of olecranon	Union of:- Upp. epiph. radius (18-20) Less. troch. femur Upp. epiph. radius (18-20) Hads phalang. foot	Union of:- Dist. extr. humer. (18-20) Less. troch. femur Upp. epiph. radius (18-20) Hads phalang. foot
23	A. of sternal end clav- icle (18-20) Union of:- Dist. extr. humerus Hads phalang. hand (18-20) Prim. centers of coxae Head femur Gr. troch. femur Low. epiph. tibia Upp. epiph. tibia (18-20) Upp. epiph. fibula (18-20)	Union of:- Dist. extr. humerus (18-19) Low. epiph. ulna Gr. troch. femur Low. epiph. femur (18-20) Upp. epiph. tibia (18-20) Upp. epiph. fibula (18-20)	A. of sternal end clav- icle (18-20) Union of:- Hads metacarpals Hads phalang. hand (18-20) Prim. centers of coxae Head femur Gr. troch. femur Low. epiph. tibia Hads metatars. (18-20)
24	U. of inf. angle scapula U. of olecranon	Union of:- Upp. epiph. radius (18-20) Less. troch. femur Upp. epiph. radius (18-20) Hads phalang. foot	Union of:- Dist. extr. humer. (18-20) Less. troch. femur Upp. epiph. radius (18-20) Hads phalang. foot
25	A. of sternal end clav- icle (18-20) Union of:- Dist. extr. humerus Hads phalang. hand (18-20) Prim. centers of coxae Head femur Gr. troch. femur Low. epiph. tibia Upp. epiph. tibia (18-20) Upp. epiph. fibula (18-20)	Union of:- Dist. extr. humerus (18-19) Low. epiph. ulna Gr. troch. femur Low. epiph. femur (18-20) Upp. epiph. tibia (18-20) Upp. epiph. fibula (18-20)	A. of sternal end clav- icle (18-20) Union of:- Hads metacarpals Hads phalang. hand (18-20) Prim. centers of coxae Head femur Gr. troch. femur Low. epiph. tibia Hads metatars. (18-20)
26	U. of inf. angle scapula U. of olecranon	Union of:- Upp. epiph. radius (18-20) Less. troch. femur Upp. epiph. radius (18-20) Hads phalang. foot	Union of:- Dist. extr. humer. (18-20) Less. troch. femur Upp. epiph. radius (18-20) Hads phalang. foot

Chart VIII  
APPEARANCE AND UNION OF BONE CENTERS  
ENGELBACH AND MCMAHON

Yrs.		Yrs.	
1	Coracoid process scapula Head of humerus (6-7 mos.) Capitate and hamate Head of femur Upper epiphysis tibia (birth) Third cuneiform	13	Lesser trochanter femur
		14	U. of heads of metacarpals (14-15 yrs.)
		15	A. of acromion Inferior angle scapula U. of centers of scapula (15-18 yrs.) A. of sternal end clavicle (15-17 yrs.) U. of heads of phalanges, hand A. of secondary centers of coxae a. Crest of ilium (15-18 yrs.) b. Acetabulum (15-16 yrs.) U. of primary centers of coxae
2	Greater tubercle humerus Capitellum, humerus Lower epiphysis radius Patella (2-3 yrs.) Lower epiphysis tibia Lower epiphysis fibula First and second cuneiforms (2-4 yrs.)	16	Union of:- Distal extremity humerus Olecranon, ulna Upper epiphysis radius Heads of metatarsals Heads of phalanges, feet
3	Oss triangularis Heads of metacarpals Heads of phalanges Heads of metatarsals (3-7 yrs.)	17	Union of:- Lower epiphysis radius Lesser trochanter femur
4	Lunate Greater trochanter femur Upper epiphysis fibula (3-4 yrs.) Navicular (tarsal)	18	Union of:- Head of humerus Head of femur Greater trochanter femur Lower epiphysis tibia
5-6	U. of head and tubercles humerus Medial epicondyle humerus Upper epiphysis radius Greater multangular Lesser multangular (6-8 yrs.) Navicular (carpal) (5-6 yrs.)	18-20	Union of:- Lower epiphysis ulna Secondary centers of coxae (20-25 yrs.) Lower epiphysis femur Upper epiphysis tibia Lower epiphysis fibula Upper epiphysis fibula
7	Lower epiphysis ulna U. of ischium and pubis Epiphysis of calcis (7-9)		
9	Pisiform (9-11)		
10	Olecranon, ulna Trochlea, humerus	22-25	U. of sternal end clavicle
11	Lateral epicondyle humerus (11-12 yrs.)		

Chart IX  
X-RAY PLATES FOR BONE DEVELOPMENT  
ENGELBACH AND McMAHON

Yrs. 1-6		Yrs. 14	Plates listed under ages 13 and 15.
6	(1) Full figure, divided on two plates.	14	(1) Clavicle.
	(2) Hands and feet, taken separately.	15	(2) Scapula.
	(3) Lateral knee for patella.		(3) Pelvis (half).
6	(1) Carpals and tarsals.		(4) Lateral foot.
	(2) Shoulder.		(5) Hand.
	(3) Pelvis.		(6) Lateral elbow.
7	(1) Pelvis.	16	Elbow (lateral).
	(2) Carpals.		(anteroposterior).
8	(1) Carpals.	17	Pelvis.
	(2) Lateral foot.	18	(1) Carpals.
9	(1) Carpals.		(2) Tarsals.
	(2) Lateral foot.		(3) Shoulder.
10	(1) Elbow (lateral).		(4) Pelvis, with hip joint.
	(2) Lateral foot.		(5) Ankle (anteroposterior).
11	Plates listed under ages 10 and 12.	19	Plates listed under ages 18 and 20.
12	(1) Elbow (lateral).	20	(1) Carpals, with wrist.
	(2) Carpals.		(2) Knee (anteroposterior).
13	(1) Hip, with half pelvis.		(3) Ankle (anteroposterior).
	(2) Anteroposterior elbow.	To 25	(1) Clavicle.
			(2) Scapula.
			(3) Pelvis.
			(4) Knee.

## 14 OSSEOUS DEVELOPMENT ENDOCRINE DISORDERS

### COMPARISON OF NORMALS WITH ENDOCRINOPATHIC SUBJECTS OF THE SAME AGE

*Birth to the age of one.* The normal infant (Fig. 1) shows the centers for the distal epiphysis of the femur, proximal epiphysis of the tibia, and three tarsal bones, the talus, cuboid,

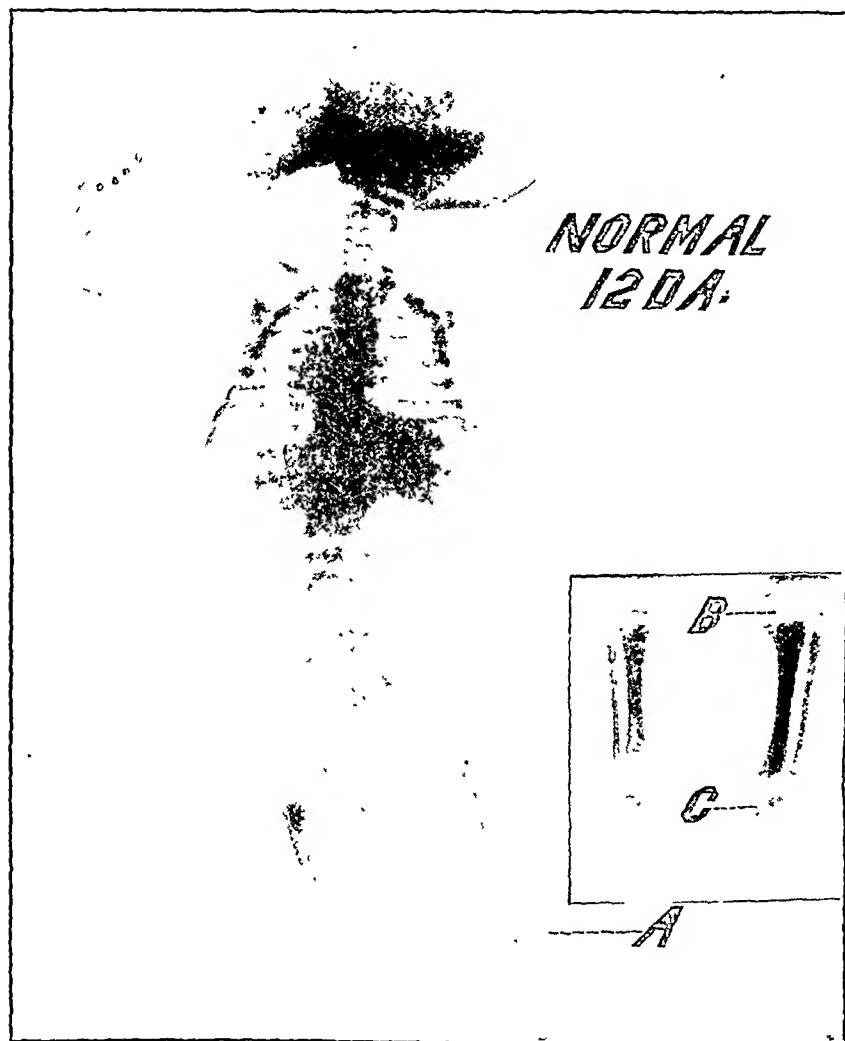


Figure 1

and calcaneus. There is absence of all carpals and heads of metacarpals and phalanges. The presence at birth of the center for the upper epiphysis of the tibia is not generally admitted by all authorities. At the age of one there are normally two carpal

centers present, the capitate and hamate. The head of the humerus, head of the femur, and third cuneiform appear within the first year. The absence of the capitate and hamate is particularly valuable in the diagnosis of early hypothyroid states. The diagnosis can thus be made at a time when material assistance

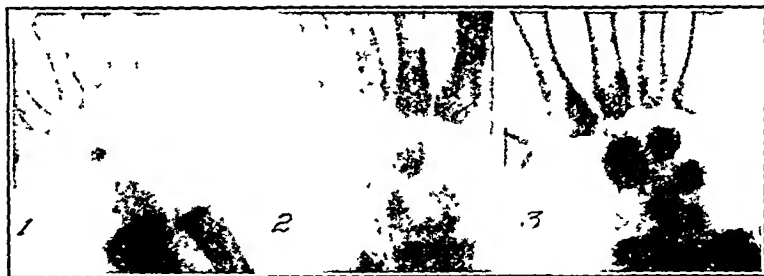
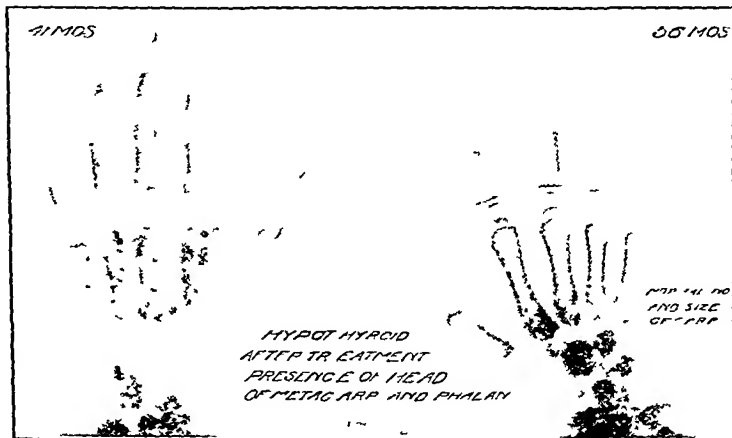


Figure 2 Effect of treatment upon hypothyroid (1) 26 months old, before treatment. Note absence of hamate, os triangularis, and head of radius (2) Same case after treatment, at 41 months. Note head of radius, capitate, hamate, os triangularis, and lunate (3) Same case at 56 months. Note enlargement of head of radius and carpal bones present in Figure 2, and presence of head of first metacarpal



can be rendered the child in the progress of normal development. For this reason, in the obstetrical department of St. John's Hospital, St. Louis, a routine radiographic examination of all infants ten days after birth, with successive radiographs taken at intervals of six months, is encouraged. This allows a study of the development of the osseous system, permitting an earlier diagnosis of endocrine disorders.



*Aged two.* The three pictures of Fig. 2 illustrate the effect of thyroid treatment upon the osseous development in hypothyroidism in infancy. No. 1 shows the hand of a hypothyroid child at twenty-six months, one carpal bone, the capitate, being present. Normally at this age there should be two carpal bones, the capitate and hamate, well developed. There is also absence of the center for the lower epiphysis of the radius, which normally appears in the second year. Other important centers occurring within the second year are the greater tubercle of the humerus, capitellum, patella, lower epiphyses of the tibia and



Figure 4 Aged 2 years, 10 months Thorax (a n, n) Enlarged thymus. Inset of hand (b) Absence of os triangularis (c) Absence of head of radius. Note absence of heads of metacarpals.

fibula, and first and second cuneiforms, these last two appearing from two to four years. No. 2 demonstrates the effect of the administration of thyroid substances upon the osseous development. At forty-one months there are four carpal bones present, together with the head of the radius. The carpal bones are slightly undeveloped, with the os triangularis and lunate of about equal size. No. 3 shows the same subject at fifty-six months. There has been definite progression in the development of the carpal bones and the head of the radius. The center for

the head of the first metacarpal is also present. This hand is practically normal for the age.

Fig. 3 is a comparison of the same hypothyroid hand after treatment. The progress of the osseous development of the hand is noted in all epiphyseal centers, particularly in the heads of the metacarpals and phalanges. The previous figure shows the absence of many centers in the phalanges at forty-one months.

*Aged two years, ten months.* Fig. 4 is a demonstration of an enlarged thymus, with underdevelopment of the carpal bones

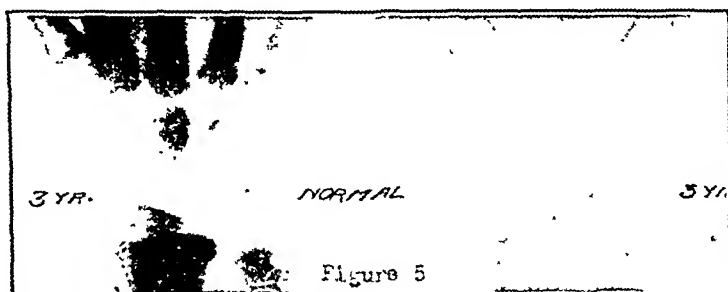


Figure 5. Carpal bones for normal, aged 3. Showing normal variation in appearance of carpal bones. Note well developed head of radius on left, and appearance of head on right. Also presence of head of first metacarpal on left, absence on right.

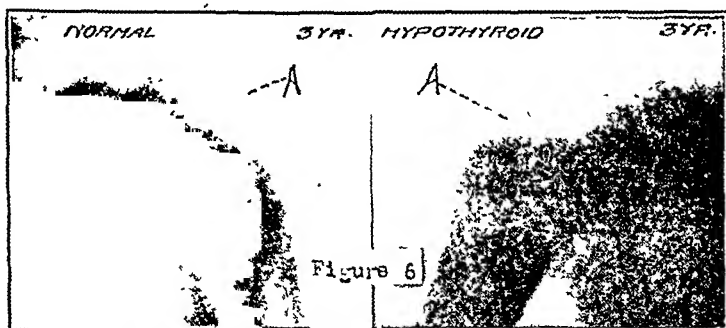


Figure 6. (1) Normal, aged 3. (A) Greater tubercle of humerus well developed. (2) Hypothyroid, aged 3. (A) Greater tubercle of humerus undeveloped.

and absence of the head of the radius. Normally at this age there should be three carpal bones present. The os triangularis is absent. Centers for some metacarpals are just appearing, which is within the normal. The heads of the phalanges are absent, these normally appearing within the third year.

*Aged three.* An example of a normal variation in the devel-

hypothyroid cases, although rather constant delayed development in the epiphyses of all long bones has been found.

A comparison of a normal with a hypothyroid shoulder at the age of four is made in Fig. 8. The greater tubercle of the humerus is normal in the picture on the left, with beginning fusion with the head. In the hypothyroid subject, the greater tubercle is undeveloped, with complete separation from the head, thus emphasizing the importance of centers other than the carpals.

A radiogram of the pelvis at the age of four (Fig. 9) demonstrates the center for the greatest trochanter of the femur (A) present in the normal subject (No. 1). This center (A) is absent in No. 2. There is also a difference in the development of the

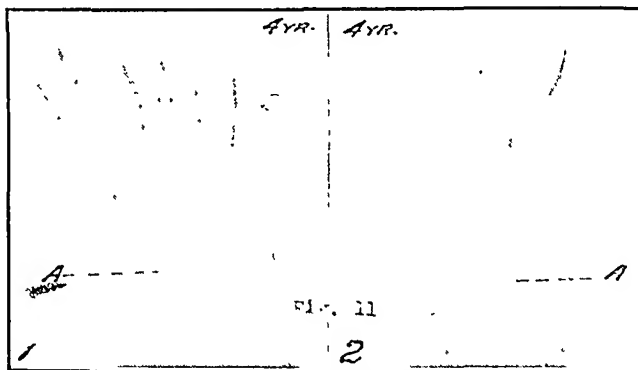


Figure 11. (1) Normal, aged 4. (A) Presence of navicular. (2) Hypothyroid, aged 4. (A) Absence of navicular. Absence of second cuneiform, with underdevelopment of all tarsals.

head of the femur. It is to be noted that the separation of the pubis and ischium is more pronounced in the hypothyroid pelvis (No. 2). These do not normally fuse until about the seventh year.

The radiograms of the knee joint at the age of four in Fig. 10 show in the normal subject on the left the presence of a fairly well developed upper epiphysis of the fibula, which normally appears between the third and fourth years. This center is absent in the hypothyroid knee on the right, and there is general underdevelopment of the other centers present, i. e., the lower epiphysis of the femur and the upper epiphysis of the tibia. This further emphasizes the point made above, that the underdevelopment of the osseous system in hypothyroidism is not limited to the carpal bones.

Fig. 11 illustrates the development of the feet at the age of four. The normal foot on the left shows the appearance of the center for the navicular, with the other tarsals well developed, the cuboid and the first, second, and third cuneiform. These last three appear within the first two years. The illustration on the right, a hypothyroid foot, shows the navicular and second cuneiform missing. The center for the first cuneiform, appearing within the second year, is faintly seen. It is to be noted that the center for the head of the first metatarsal is also undeveloped, as contrasted with the normal foot. The hypothyroid foot represents about a two-year development.

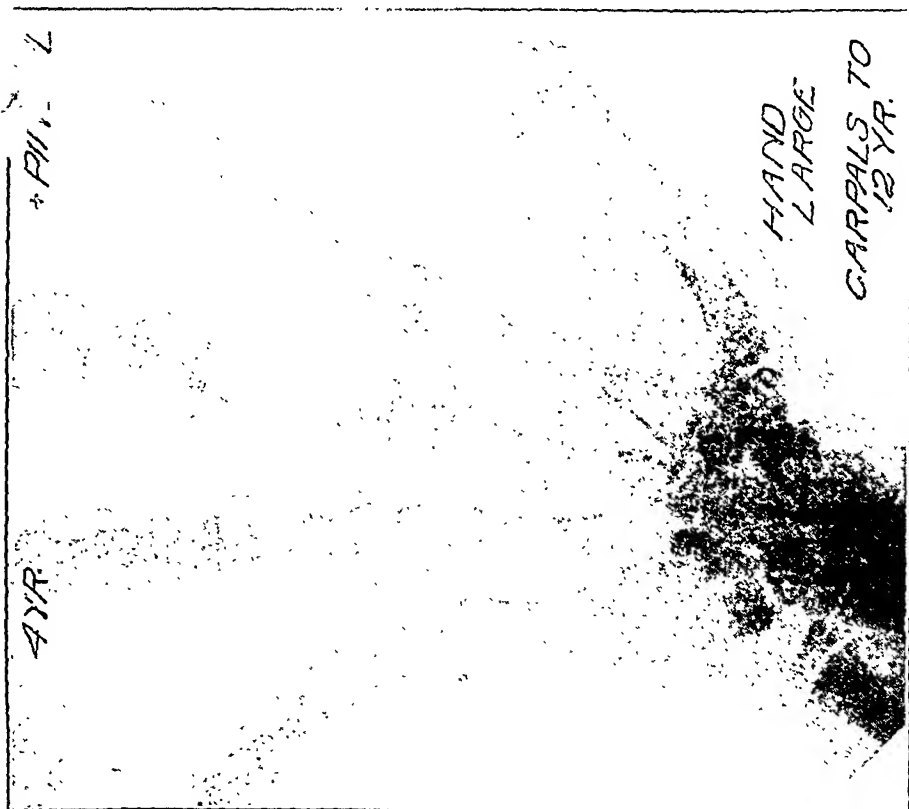
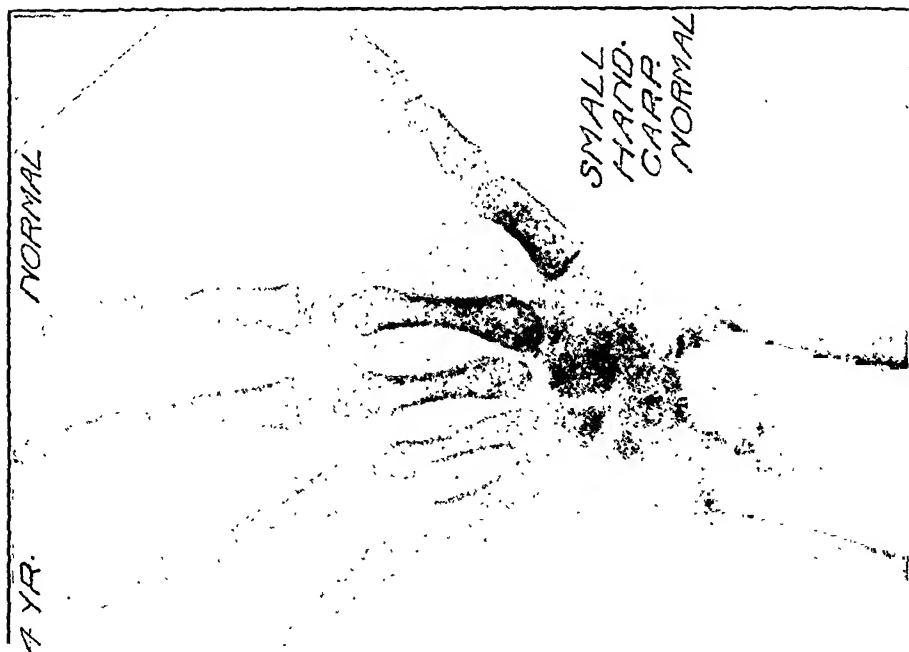
Fig. 12 is a radiogram of the carpal bones of a subject aged four with a clinical diagnosis of hypothyroidism. It is interest-



Figure 12. Aged 4. Clinical diagnosis, hypothyroid, doubtful because of advanced carpal development for age. Presence of navicular and lesser multangular. (A) Accessory head of second metacarpal.

ing to note that there is an overdevelopment of the carpal bones, the six present being the capitate, hamate, os triangularis, lunate, navicular, and lesser multangular. There is also an accessory head of the second metacarpal. The hand represents about a six-year development. It is in these cases that the study of the osseous development assumes importance for diagnostic purposes. We assume a pluriglandular involvement, which may account for the advanced carpal development, not typical of the true cretin.

In Fig. 13 the hand of a normal four-year child is contrasted with that of a subject with suspected hyperpinealism.



The normal hand is smaller than the comparison hand, while the carpal bones are present for the age. The suspect hyper-pineal hand is developed to the age of twelve, with all the car-

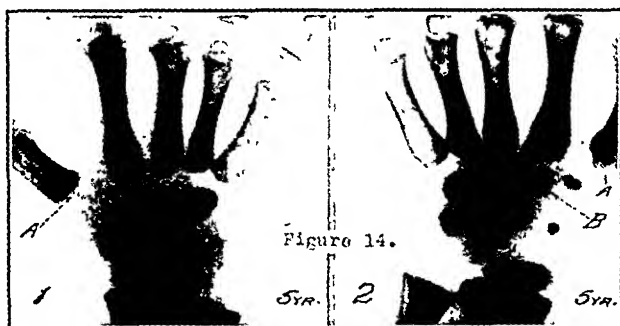


Figure 14. (1) Hypothyroid, aged 5. Carpals for age absent—os triangularis, lunate, navicular, and greater multangular. Head of first metacarpal absent. (2) Advanced carpal development for age, lesser multangular present. Head of first metacarpal present.

pals present, including the pisiform. The heads of the metacarpals and phalanges are likewise well developed, together with the heads of the radius and ulna.

*Aged five.* In Fig. 14 the hypothyroid hand (plate No. 1) is developed to the age of two, with three carpal bones absent,

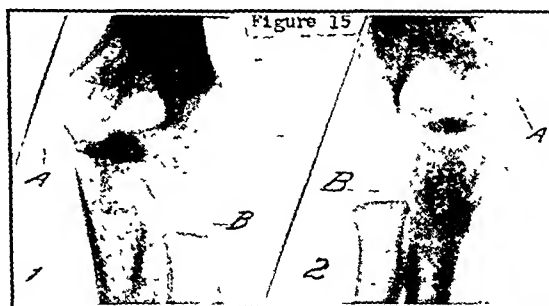
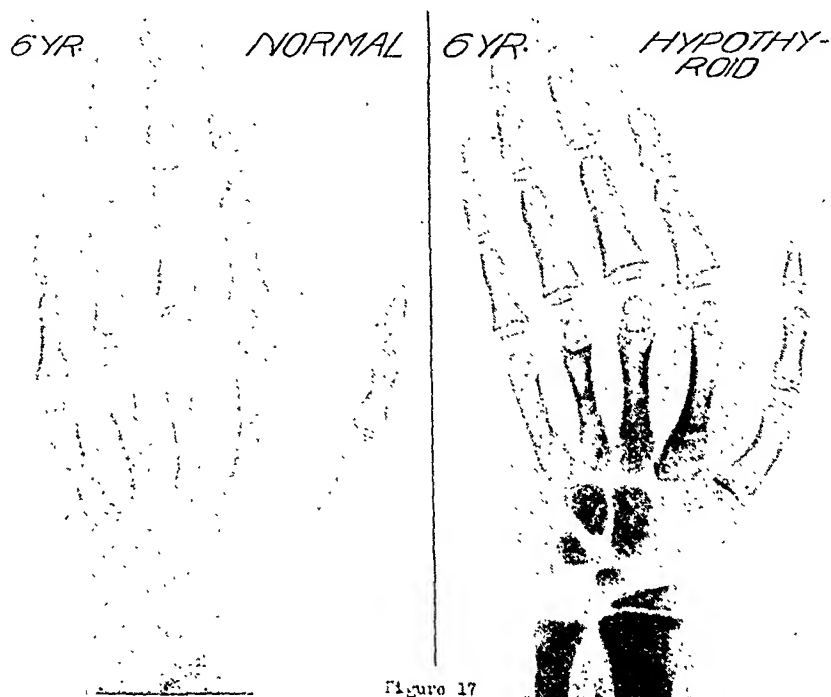
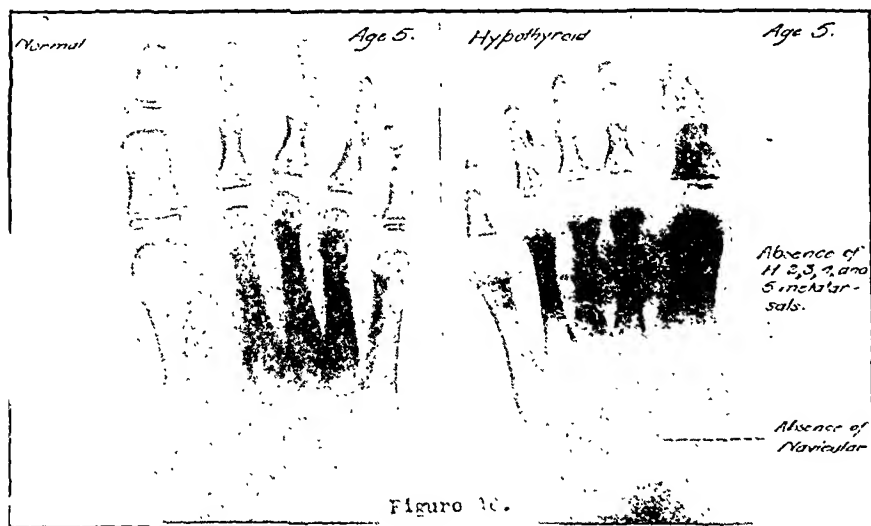


Figure 15. (1) Normal, aged 5. (2) Hypothyroid, aged 5. Note absence of internal condyle of humerus and head of radius in Figure 2.

the os triangularis, os lunatum, and navicular; while plate No. 2 shows a normal variation in the carpal development for the age of five, with no obvious endocrine dysfunction to account for the slightly advanced development. The heads of the metacarpals of the hypothyroid hand are developed to the age of three. It is to be noted in Plate No. 2 that all the carpal centers are present except the pisiform. The os triangularis and os lunatum are not

fully developed for the age. The head of the radius is well developed.

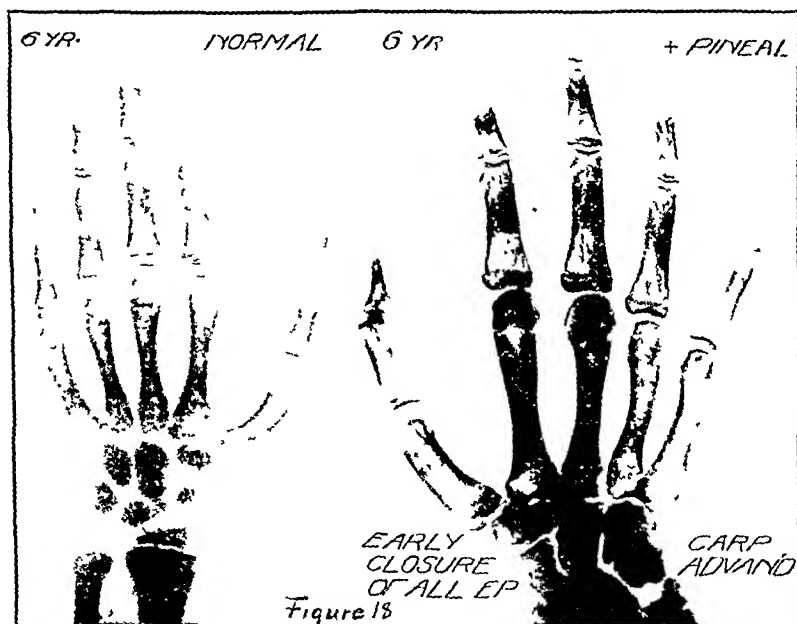
Plate No. 1 (Fig. 15) is the elbow of a normal five-year-old



child. Plate No. 2 is an elbow of a hypothyroid child of the same age. In the normal subject on the left the centers for the

medial epicondyle and head of the radius are present, the latter just appearing, while the capitellum is well developed. In the hypothyroid subject there is an absence of these centers, together with underdevelopment of the capitellum. The difference in size and density of the bones is to be noted.

Fig. 16 is a comparison of the foot of a hypothyroid child of five years with that of a normal child of the same age. In the



hypothyroid foot on the right the navicular and the heads of the second to the fifth metatarsal, and many of the phalangeal heads are absent. The second cuneiform is undeveloped. This foot represents about a three-year development.

*Aged six* In Fig. 17 the same underdevelopment of the carpal is seen in the hypothyroid subject on the right as has been found at other ages. The navicular and the greater and lesser multangulars are absent, together with delay in development of the heads of the metacarpals and phalanges. The carpals present are developed to the age of four.

A case of suspected hyperpinealism at the age of six is contrasted with the normal condition for the same age in Fig. 18. The carpal bones, metacarpals, and phalanges are large, devel-



oped to about the age of fourteen, with beginning closure of all epiphyseal lines, particularly evident in the metacarpals. The head of the ulna, which is absent in the normal, is well developed in the subject with suspected pinealism. This overdevelopment of the osseous system for the age is characteristic of this type of case. Early closure of the epiphyseal lines is a constant feature. The same advanced development may be seen in the other epiphyses about the body. It is unusual in these cases to find the epiphyseal lines open after the fifteenth year. The epiphyseal lines of the long bones normally close at about the eighteenth year.

In Fig. 19 are two elbows. No. 1 on the left is that of a normal subject aged six, while No. 2 on the right is that of a hypothyroid. In the normal elbow on the left the medial api-

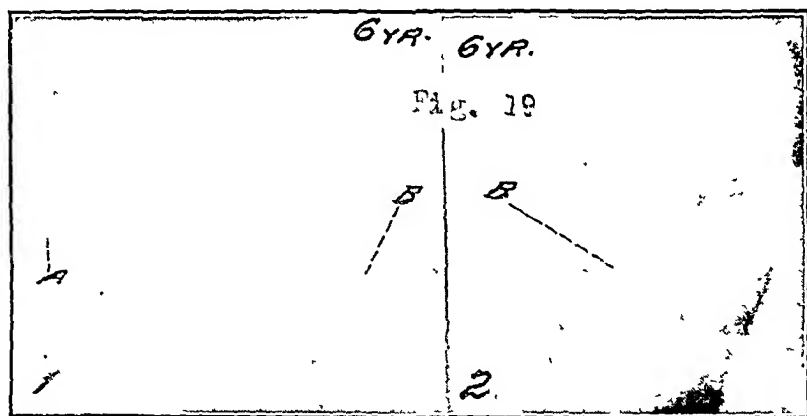


Figure 19 (1) Normal, aged 6 (A) Appearance of medial epicondyle. (B) Presence of head of radius. (2) Hypothyroid, aged 6. (B) Absence of head of radius. Absence of medial epicondyle. Note difference in size of bones.

condyle is faintly visible, while the head of the radius is fairly well developed. These are absent in the hypothyroid elbow on the right. There is a general underdevelopment of the bones in the latter.

*Aged seven.* In Fig. 20 the hypothyroid subject on the right again demonstrates the underdevelopment of the carpals. The normal subject on the left shows all carpal centers present and well developed, with the head of the ulna likewise present. This is the earliest age at which the writers have found this center appearing, although most authorities state that it appears one or two years earlier. The hypothyroid subject on the right shows underdevelopment of the carpal bones, which the writers have

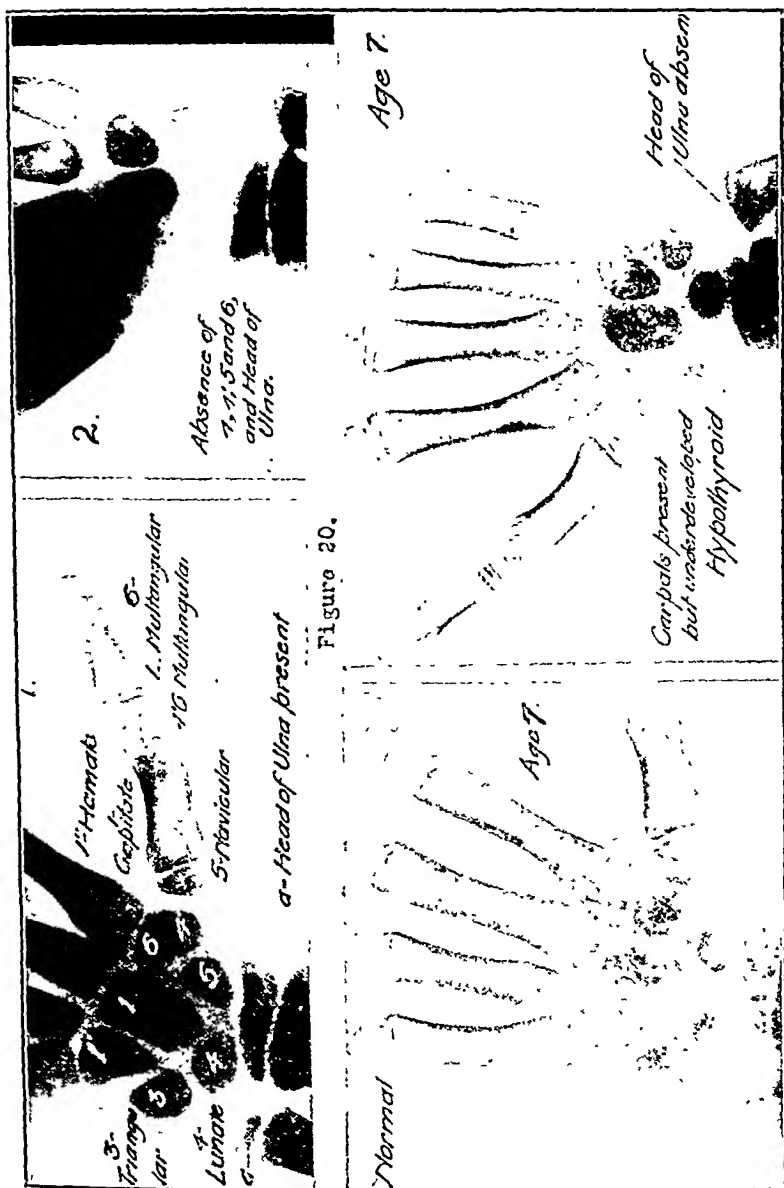


Figure 21

Figure 20. (1) Normal, aged 7. All carpals present and well developed. Head of ulna present. (2) Hypothyroid, aged 7. Three carpals present; carpals absent Nos. 4, 4', 5 and 6. Head of ulna absent.

Figure 21. Comparison of hypothyroid, age 7, with normal, age 7, on left.

found so constantly in these cases. There is an absence of the head of the ulna. The hand is developed to about three years

The carpal development in the hypothyroid hand in Fig. 21 at age seven might well be contrasted with that of the hypo-

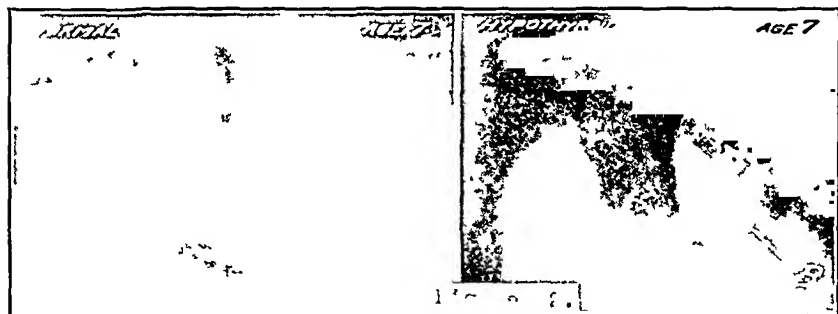


Figure 22 Normal shows (A) Union of pubis and ischium Hypothyroid shows (B) non union of pubis and ischium

thyroid in Fig. 20 The difference between the two is evident. In that of Fig. 21 we have all the centers present for the age, but not developed to normal size. The head of the ulna is

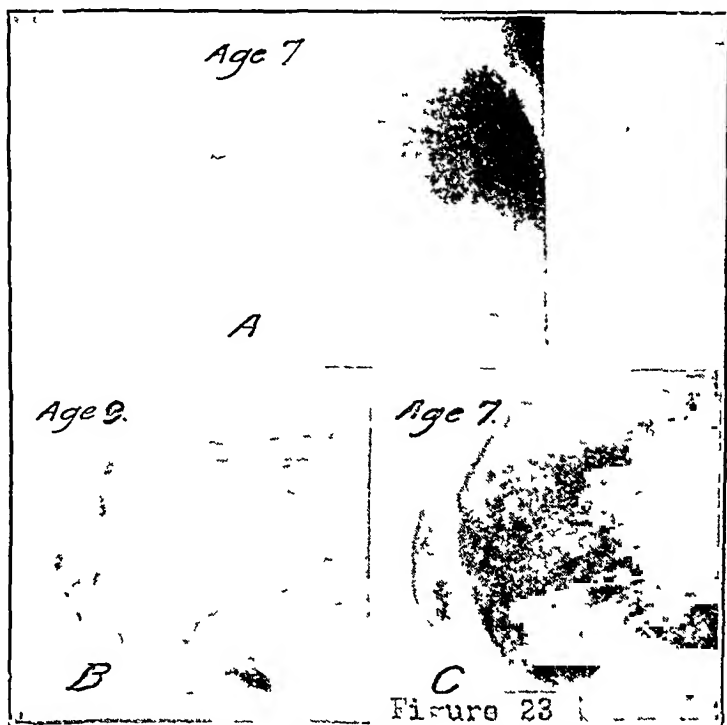


Figure 23 (A) Normal aged 7 Absence of epiphyseal head of calcaneus (os calcis) (B) Aged 9 Appearance of epiphyseal head of os calcis (occurs normally at 7 to 5) (C) Aged 7 Presence of head of os calcis

absent. The heads of the metacarpals and phalanges show the same underdevelopment. Clinically this case is one of hypothyroidism. The importance of radiographic examination in these cases of minor deficiency cannot be over-emphasized, for where clinical characteristics are absent, it is frequently possible to make a diagnosis from the radiographic examination.

A radiogram of the pelvis of a hypothyroid subject, aged seven, contrasted with the normal pelvis in Fig. 22, shows separation of the pubis and ischium in the hypothyroid on the right, while fusion of the two bones is complete in the normal on the left. This fusion has been found to occur normally at this age.

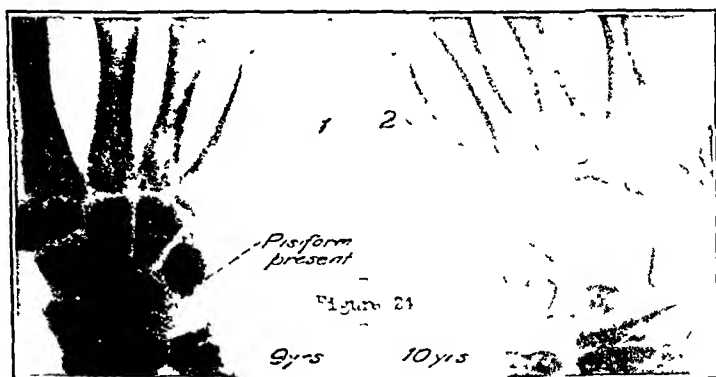


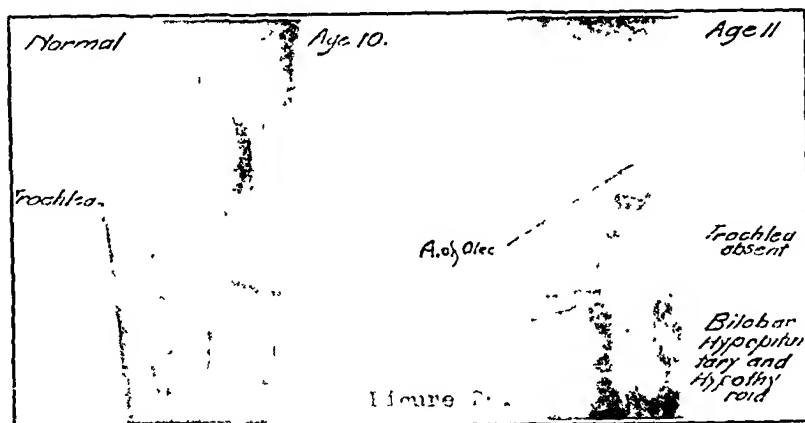
Figure 24 (1) Thyro-pituitary insufficiency (aged 9). Note presence of pisiform (2) Hypothyroidism (aged 10) Note absence of pisiform

The hypothyroid pelvis represents a development of about five years.

*Aged seven to nine.* The radiogram in Fig. 23 shows the variations that occur in the appearance of the center for the epiphysis of the calcaneus. This normally appears between seven and nine years. In A, at the age of seven, it is absent, while in B, at the age of nine, the center is just appearing, being well developed in C, at the age of seven, probably appearing at about the sixth year in this patient. In this last case the other epiphyseal centers about the body were developed to a degree normal for the age.

*Aged nine and ten.* The pisiform is present in No. 1 (Fig. 24), the hand of a patient aged nine with thyro-pituitary insufficiency, while it is absent in the hypothyroid subject (No. 2) aged ten. This, together with a general tendency toward slight

advancement in the carpal development, has been found frequently in these cases. The carpal bones in the thyro-pituitary insufficiency are denser than those of the hypothyroid patient, with more tendency to massing. The pisiform appears normally between nine and eleven years.



The elbow of the thyro-pituitary subject (Fig. 25, No. 1) at nine years gives evidence of the tendency to slightly advanced osseous development, as has been seen in Fig. 24. This is apparent in the appearance of the lateral epicondyle of the humerus

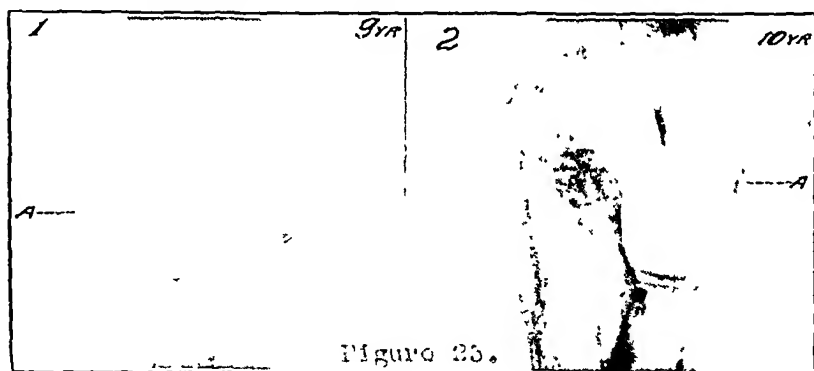
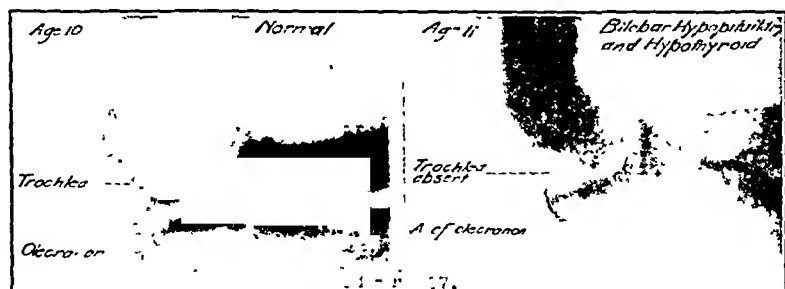


Figure 25. (1) Thyro pituitary, 9 years. (A) Well developed lateral epicondyle. Note well developed olecranon (2) Normal, 10 years. (A) Appearance of lateral epicondyle. Olecranon small.

and well developed olecranon and trochlea, while in the normal child (No. 2) of ten years the center for the lateral epicondyle is just appearing. This has been found present normally from ten to twelve years. The center for the olecranon is about the size for the age, the center for the trochlea being absent. This last appears about the tenth year.

*Aged ten and eleven.* In Fig. 26 the elbow of a subject, aged eleven, with a pluriglandular (pituitary-thyroid) deficiency is compared with the elbow of a normal child, aged ten. We have mentioned above in Figs. 24 and 25 that the thyro-pituitary subject shows a tendency to a slight advance in the osseous development, as contrasted with the pure thyroid. This



advanced development has been seen chiefly in the carpals and centers for the long bones. The subject with pituitary-thyroid deficiency,\* on the other hand, shows a tendency to a slight delay

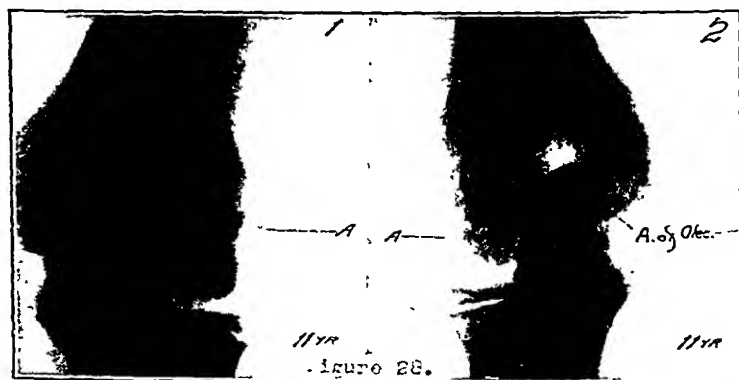
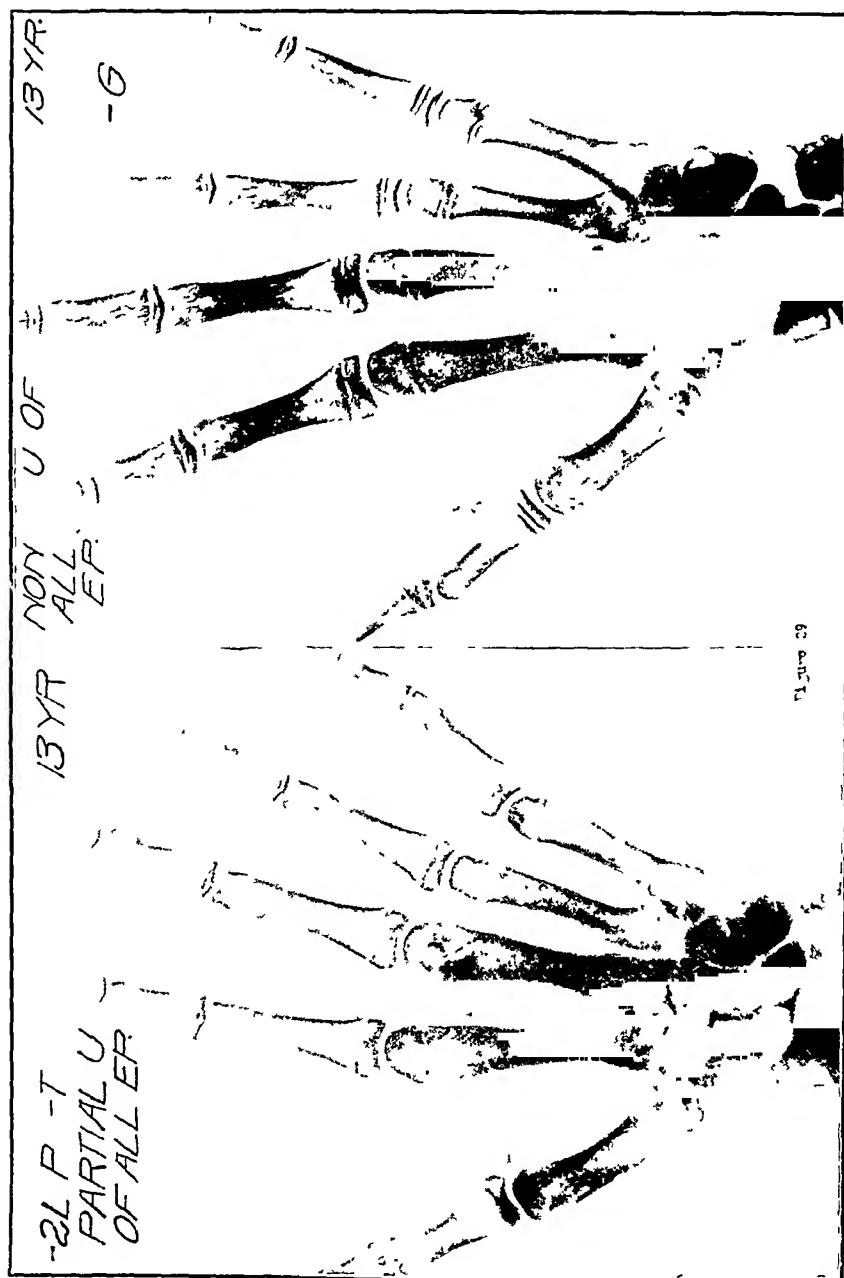
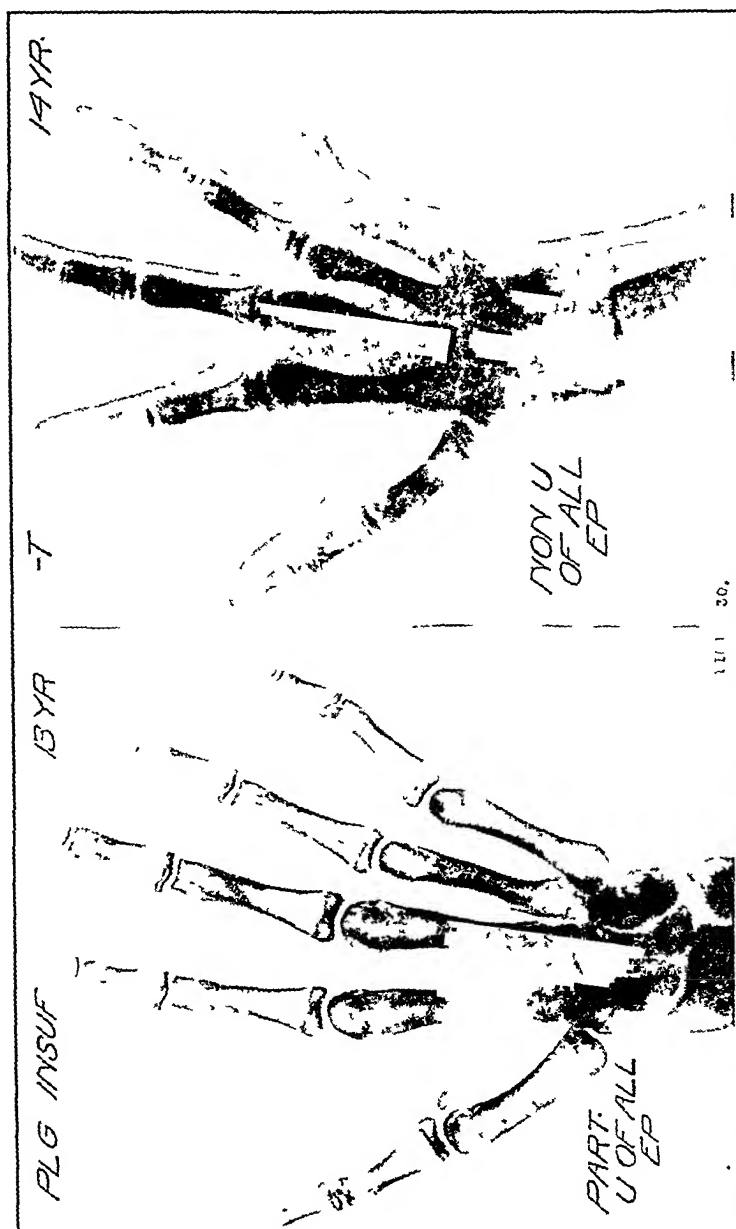


Figure 28. Aged 11. (1) Normal. (A) Appearance of lateral epicondyle of humerus. (2) Pluriglandular, bilobar hypopituitarism, with hypothyroidism (A) Absence of lateral epicondyle of humerus.

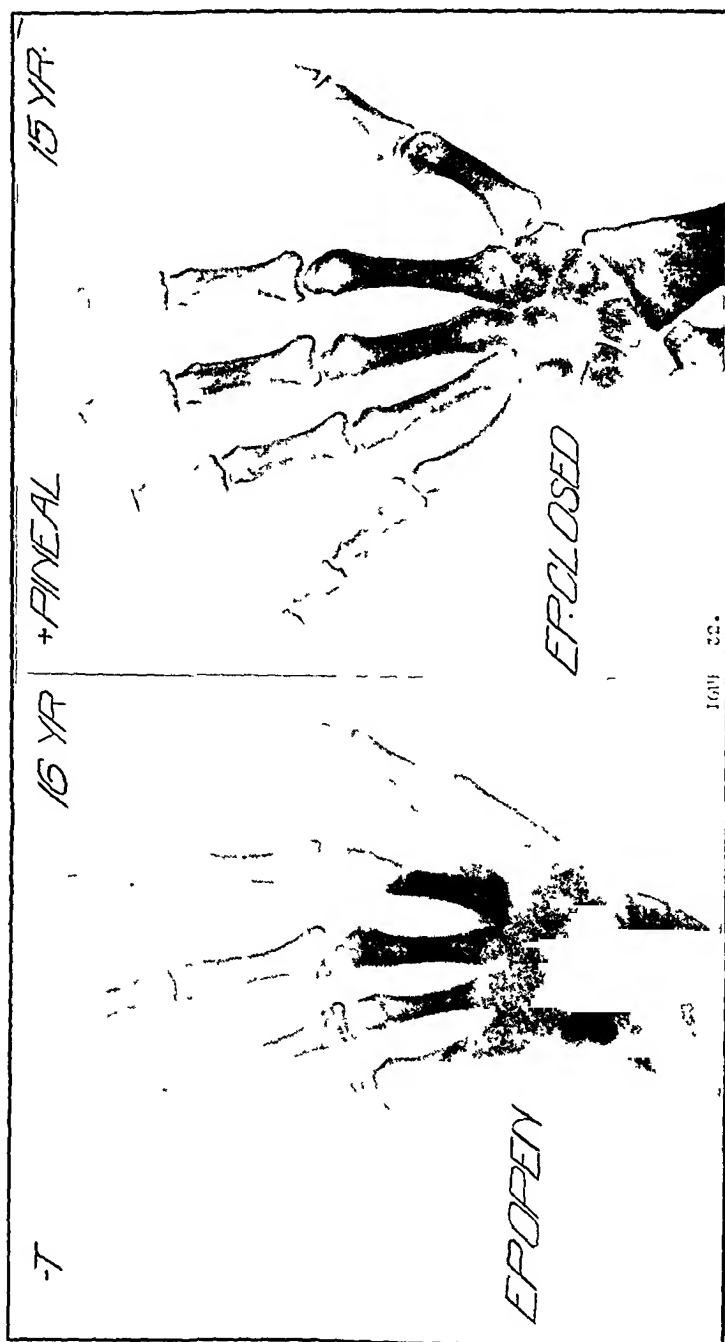
in the development of these centers. These points have been brought out in a limited series of cases, and suggest further study, with the confirmation of additional cases. The delayed development is seen in Fig. 26, in which the trochlea is absent in the pituitary-thyroid, and well developed in the normal subject.

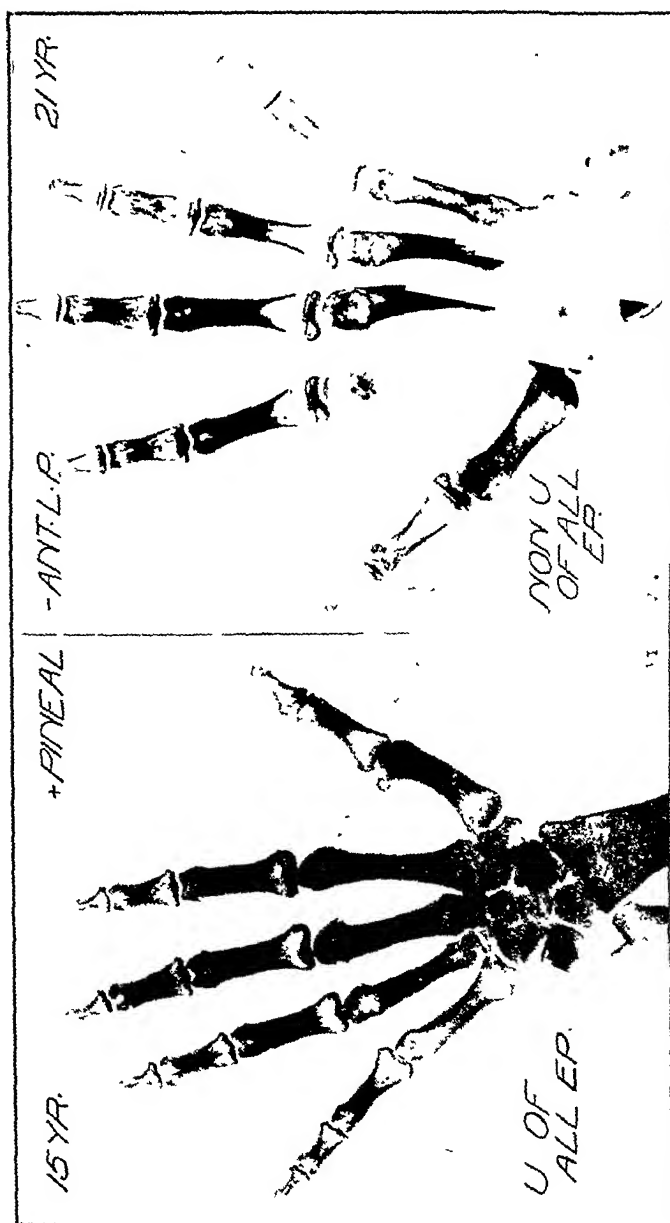
\*The distinction between thyro-pituitarism and pituitary-thyroidism lies in the fact that in the former there is early hypothyroidism, with a subsequent pituitary deficiency, while in the latter the pituitary deficiency antedates and is complicated by the thyroid deficiency.



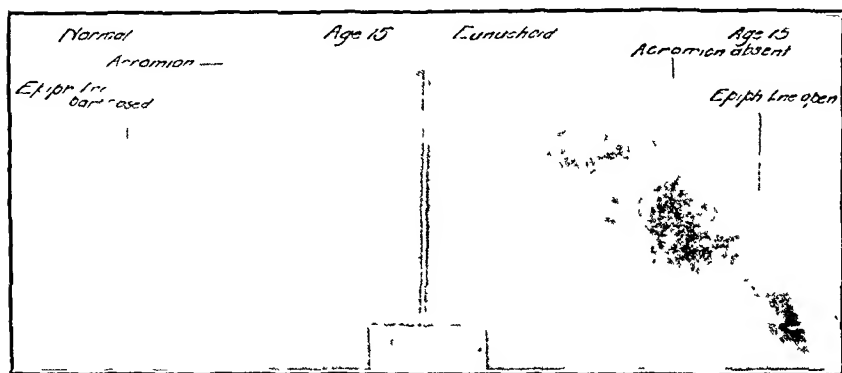








but slightly larger than the pineal hand. There is, however, a persistence of all epiphyseal lines in the former, including the epiphyses of the radius and ulna, which normally close between seventeen and nineteen years. We have a contrast of early closure of epiphyseal lines and delayed closure in two subjects who from the standpoint of stature resemble each other closely but who differ widely in many important characteristics, such as mentality, the development of the primary and secondary sexual characters, etc. The etiological factor of the decreased stature in one is essentially different from that in the other. The early closure of epiphyseal lines in the suspected hyperpineal hand prevents normal growth, while the absence of the anterior lobe



pituitary secretion does not permit the normal growth of the long bones in this type of case, so that the stature remains small in spite of the fact that all epiphyseal lines remain open.

In Fig. 34 the shoulder of a normal subject aged fifteen is contrasted with the eunuchoid shoulder of the same age. The center for the acromion is present in the shoulder on the left, and there is beginning closure of the epiphyseal line of the head of the humerus. Normally the head of the humerus is completely fused with the shaft at the eighteenth year. The eunuchoid subject on the right shows an absence of the epiphysis of the acromion, with the epiphyseal line of the head of the humerus completely open. This delay in the closure of the epiphyses is, as mentioned above, characteristic of the hypogonad or eunuchoid type.

*Aged sixteen.* The center for the crest of the ilium is shown well developed in Fig. 35. This normally appears at the fifteenth year, together with the other secondary centers of the os

coxae. Other osseous findings at the age of fifteen to sixteen are the appearance of the sternal end of the clavicle, union of

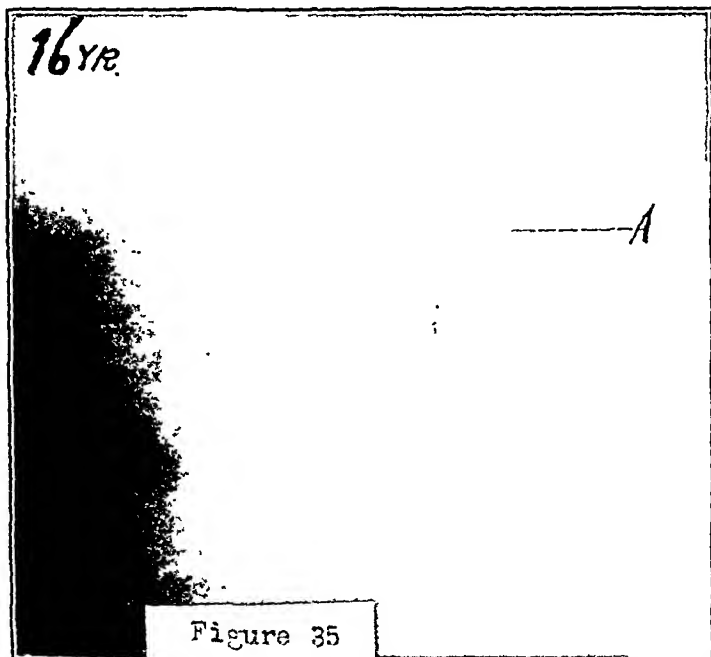


Figure 35. Bilobar hypopituitarism, aged 16 (A) Crest of ilium well developed (normal at 15).

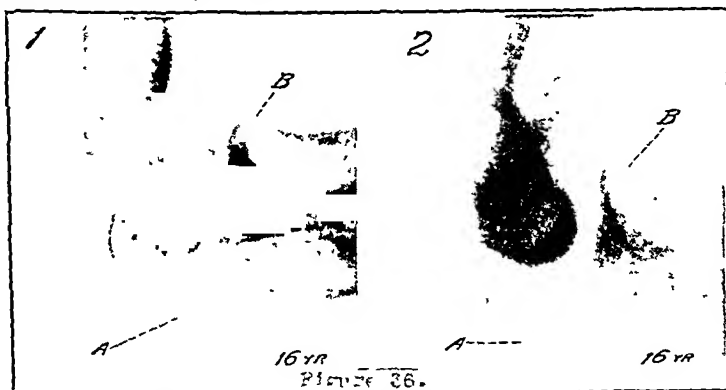
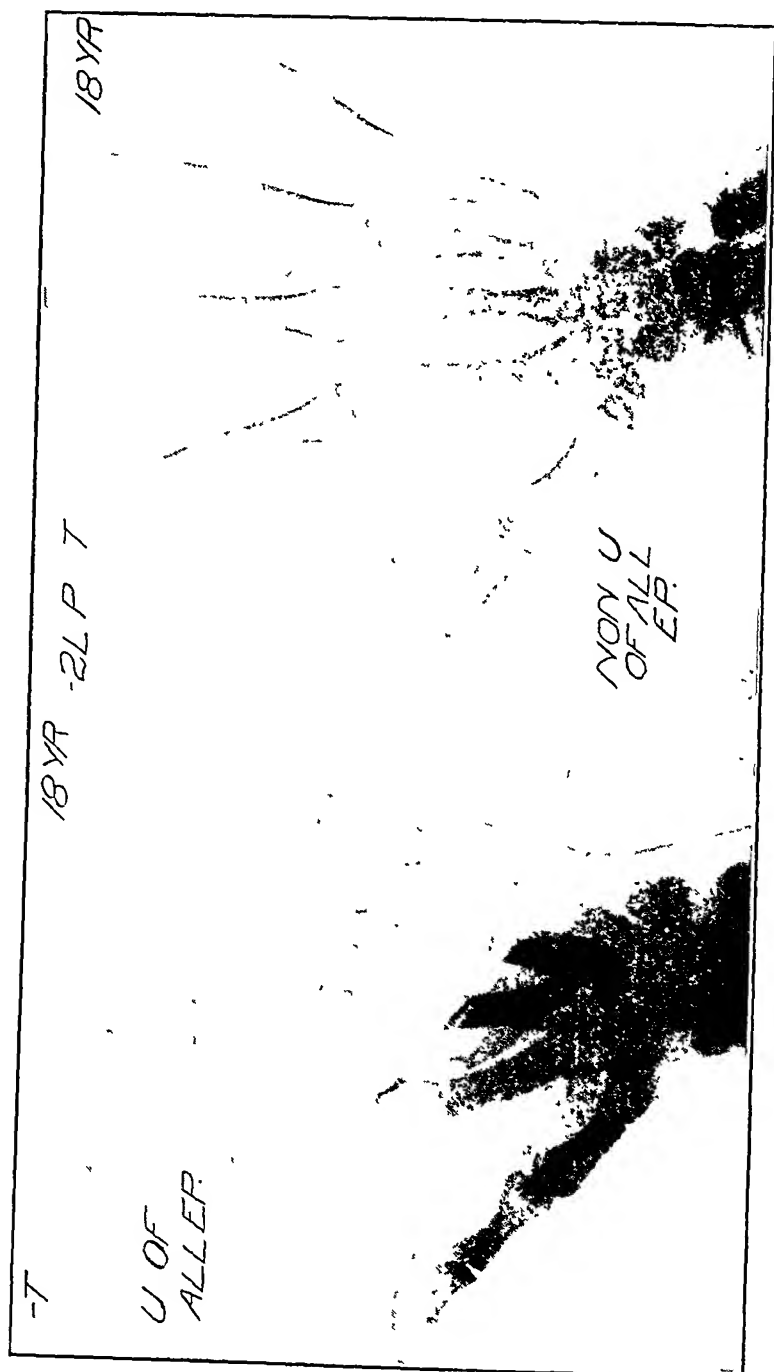
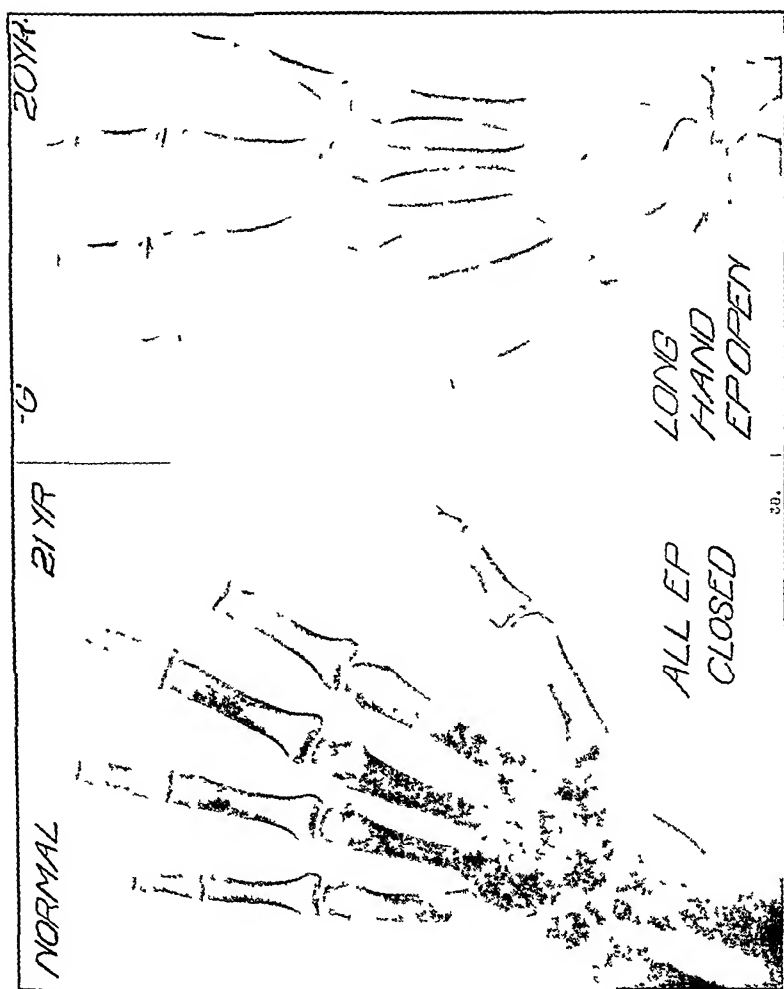


Figure 36. Aged 16 (1) Normal, showing (A) olecranon closed; (B) head of radius closed. (2) Hypopituitarism, preadolescent, showing (A) olecranon open; (B) head of radius open.

the heads of the phalanges of the hand, and union of the primary centers of the os coxae.

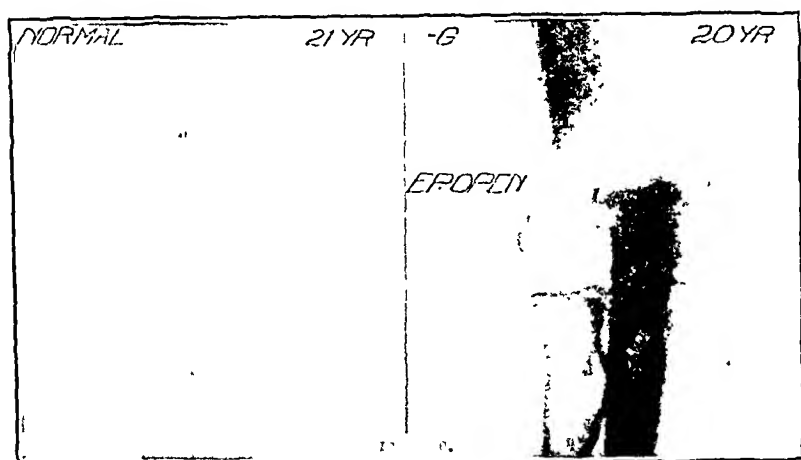
In Fig. 36 is seen other evidence of the delay in the closure





of the epiphyseal lines in the subject with anterior lobe pituitary deficiency. The normal elbow on the left of a subject aged sixteen shows complete closure of the olecranon and practically complete closure of the epiphyseal line of the head of the radius. The elbow of the patient with anterior lobe deficiency shows the epiphyseal lines open. The same delay in closure is seen in the distal epiphysis of the humerus, this normally closing at about sixteen years.

*Aged eighteen.* The subject with pluriglandular deficiency (pituitary-thyroid) in Fig. 37 shows a delay in the closure of all epiphyseal lines, the epiphyseal lines of the metacarpals and phalanges normally closing at fifteen to sixteen years, while the epiphyseal lines of the radius and ulna, which are still present



in this hand, normally close between the seventeenth and nineteenth years. The hypothyroid hand on the left shows closure of all epiphyseal lines, which is normal for the age. The hands resemble each other very closely in size.

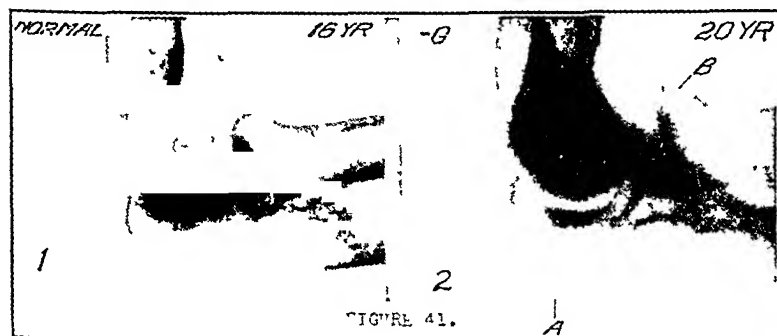
*Aged twenty.* The hypogonad hand on the right in Fig. 38 shows a general increase in length, with a persistence of the epiphyseal lines of the metacarpals, phalanges, radius, and ulna. The hand is slender, the increase in length being accounted for by the failure of the epiphyseal lines to close, as they do normally between the fifteenth and nineteenth years. The normal hand on the left shows all epiphyses closed.

The radiograms of the elbows of the same subjects as seen in Fig. 38 are contrasted in Fig. 39. All epiphyses are closed in the normal elbow. There is complete fusion of the separate

centers of the distal extremity of the humerus, together with fusion of the distal extremity of the humerus with the shaft. The olecranon and the head of the radius are closed, these normally closing from the sixteenth to the nineteenth years. These epiphyses are frankly open in the hypogonad elbow on the right.



The radiograms in Fig. 40 are those of the same hypogonad subject taken after an interval of one year. The outstanding feature is a persistence of all epiphyseal lines of femur, tibia, and fibula at the age of twenty. There apparently has been no



tendency for the epiphyseal lines to close in the interval elapsing between the first and second radiograms, taken at nineteen and twenty years respectively. The delay in closure of the epiphyseal lines is seen in all the long bones, with resultant increase in stature due to a preponderance of long bone development.



In Fig. 41 the epiphyses of the elbow of a hypogonad subject aged twenty are contrasted with those of a normal subject aged sixteen. In the latter the epiphysis of the olecranon is closed and the head of the radius practically closed. In the former the epiphyses are open.

The pelvis in Fig. 42, showing the head of the femur in a hypogonad subject of twenty, gives additional evidence of the delayed closure of the epiphyses, and contrasts strongly with the suspected hyperpineal subject of fifteen on the right, in which all epiphyses are closed, a point emphasized in the earlier figures. The clinical types differ markedly in somatic and genital development.

-G  
20 YR

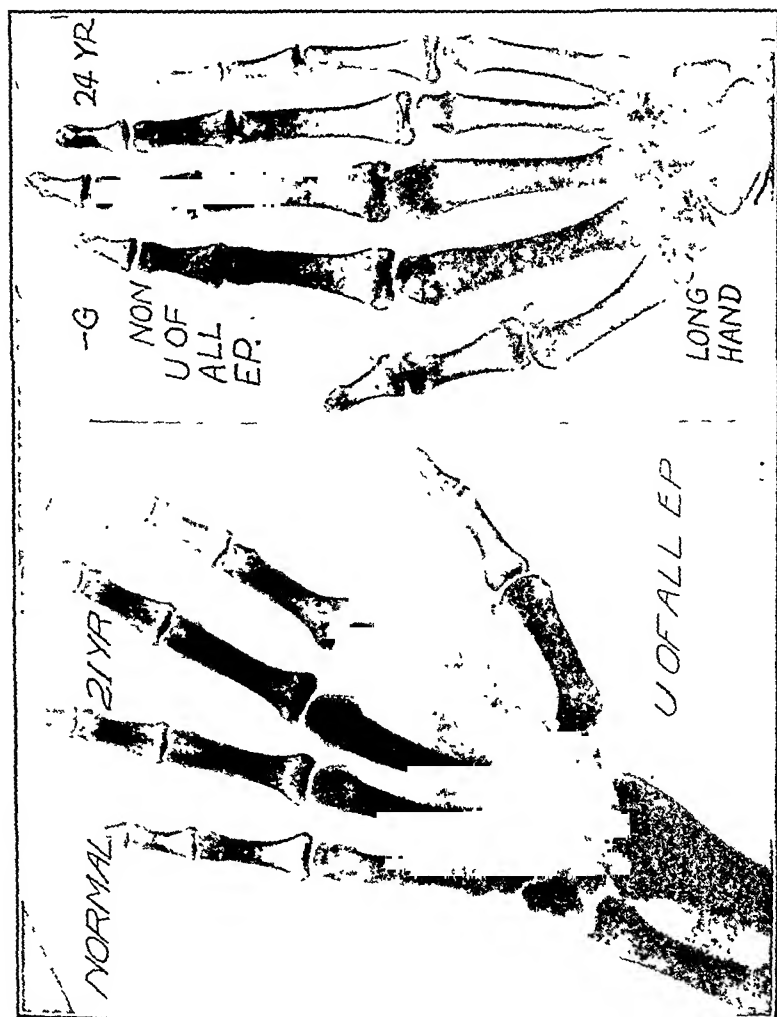
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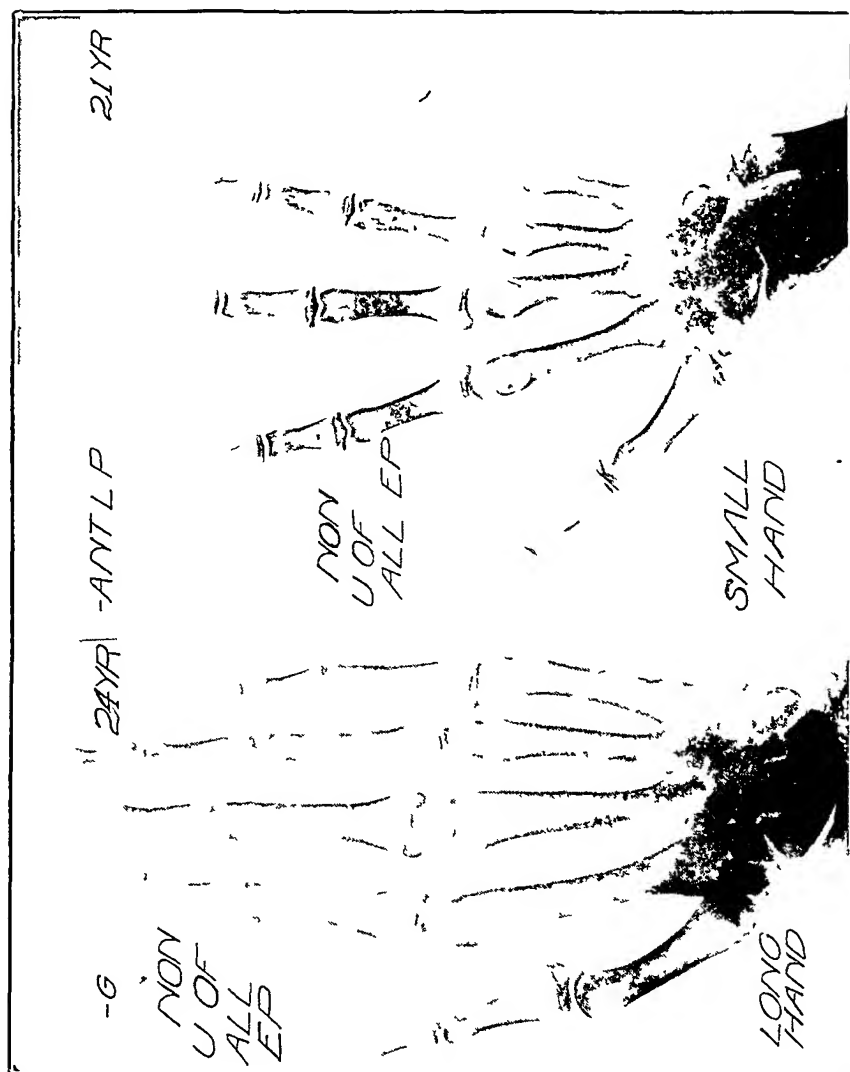
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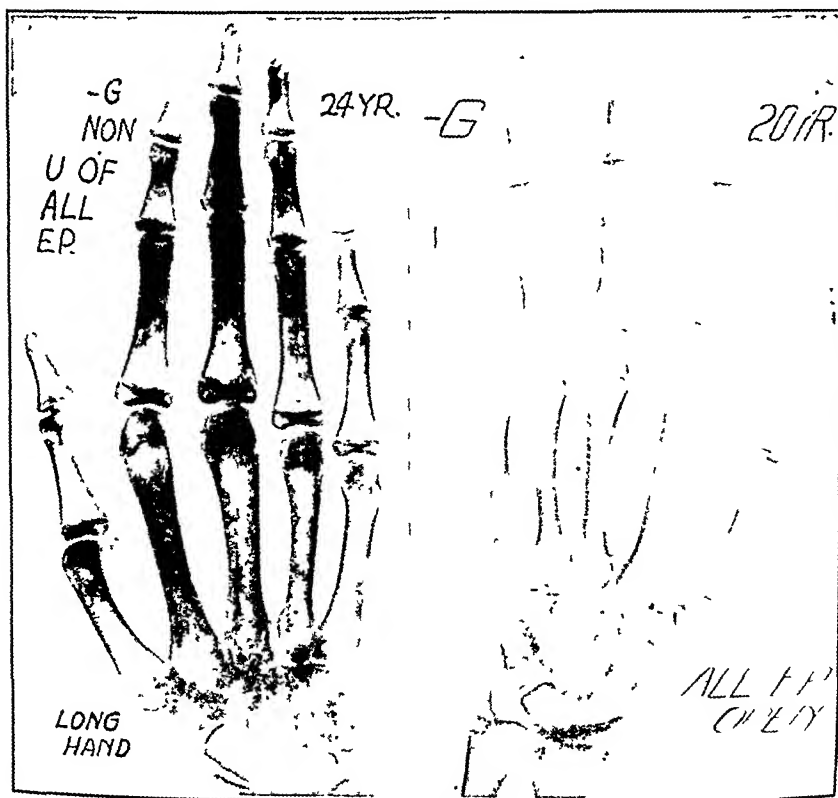
*Aged twenty-four.* In Fig. 43 the hand of a hypogonad subject aged twenty-four is contrasted with that of a normal subject aged twenty-one. The same characteristics of hypogonad development, the size and type of hand, the open epiphyses, etc., as manifested in the above comparisons, are evident in the picture on the right. It is to be noted that the hypogonad patient in this figure is four years older than the hypogonad patient shown previously, and yet there is no evidence of closure of the epiphyses.

In Fig. 44 we compare a hypogonad hand, aged twenty-four, with that in a case of anterior lobe pituitary deficiency at the age of twenty-one. The difference in size of the hands is manifest. In the hypogonad subject we have the slender, artistic "eunuchoid" hand, while in the anterior lobe deficiency we have the small, fragile hand, the type "en petite." In both, we have





a persistence of the epiphyseal lines. In the former we have overgrowth of the long bones, and in the latter underdevelopment of the long bones. Clinically the types are distinct. The size of the hand, apart from the stature and general bodily configuration, is sufficient to differentiate the two types, although the epiphyseal lines are persistent in both



*Aged twenty-four and twenty.* A comparison of two hypogonad hands is seen in Fig. 45, both hands of a classical type, with the epiphyseal lines clearly open three to six years beyond the normal age.

*Aged twenty-one.* The radiograms of the knee joints of a subject aged twenty-one with anterior lobe pituitary deficiency and a subject with hypogonadism aged twenty display the characteristics which have been evidenced in the above figures, in the persistence of the epiphyseal lines seen in the hands and other

# 48 OSSEOUS DEVELOPMENT ENDOCRINE DISORDERS

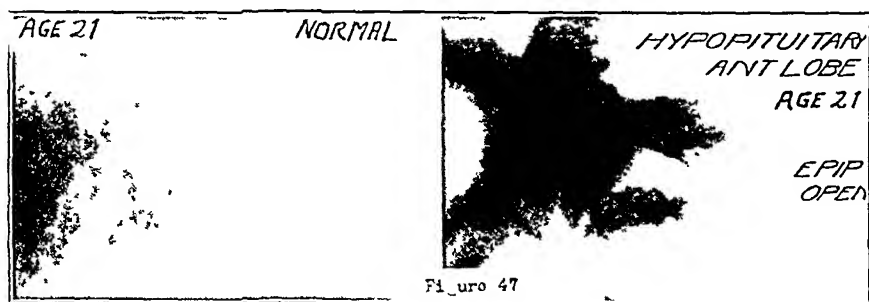
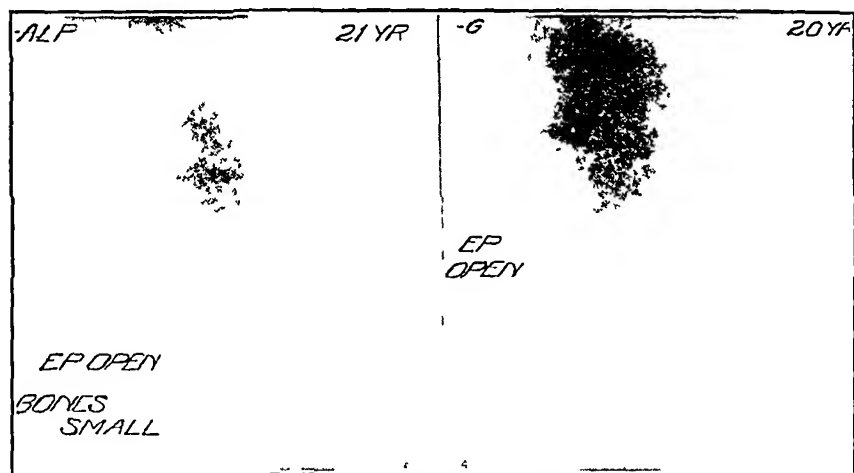
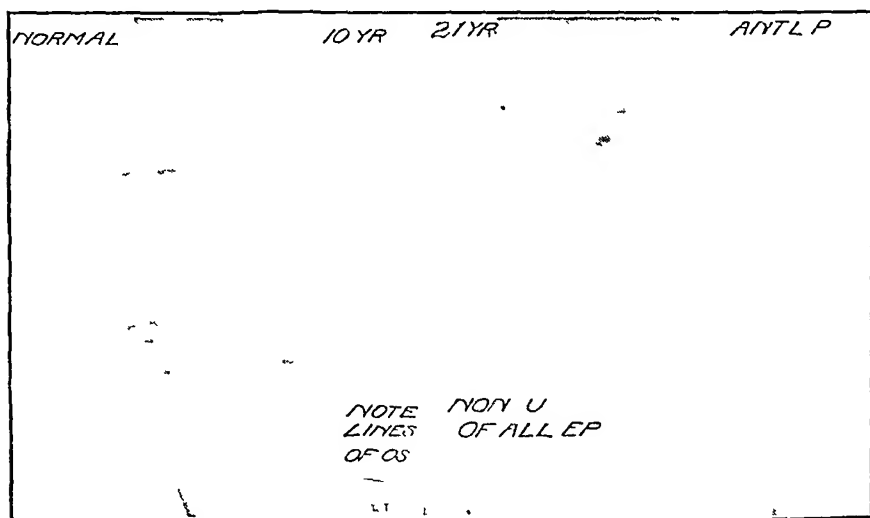


Figure 47 Normal aged 21 showing epiphysal line of humerus closed. Hypophysitary anterior lobe deficiency, aged 21, showing epiphysal line of humerus open



long bones. There is a marked difference, however, in the size of the long bones and the size of the corresponding epiphyses.

The normal subject aged twenty-one in Fig. 47 shows complete closure of the epiphyseal line of the head of the humerus, this normally closing about the eighteenth year. In the anterior

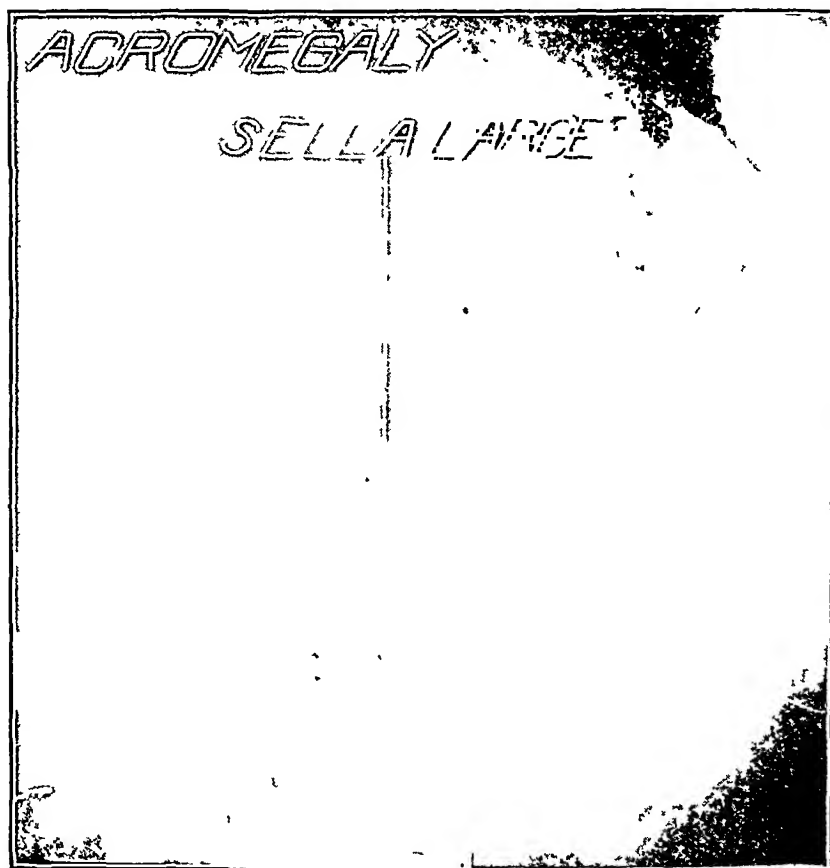


lobe pituitary deficiency there is a persistence of the epiphyseal line of the head of the humerus.

In Fig. 48 the osseous development of the knee in anterior lobe deficiency at the age of twenty-one is seen to be that of about ten years. There is a close resemblance between these

radiograms, as evidenced in the epiphyseal lines, size of the bones, etc. The lines of ossification are to be noted in the normal ten-year knee on the left.

*Acromegaly.* In Fig. 49 note the characteristic spade hand of the acromegalic, showing the well known tufting of the distal phalanges, with hook formation of the distal phalanx of the thumb, the prominence of the tuberosities of the metacarpals and phalanges, the increase in breadth of all bones, and the thickening of the cortex.



The radiogram (Fig 50) of the sella turcica of the same patient whose hand is presented in Fig. 49 shows that the sella is definitely enlarged, without evidence of erosion. There is a thickening of the bones of the skull, with an enlargement of all sinuses, seen particularly in the frontal sinuses.

*Aged twenty-five.* The hand of a giant in Fig. 51 shows marked increase in growth of all bones. The hand is extremely large, the palm being narrow in proportion to the length of the



fingers. It is to be noted that there is absence of tufting of the distal phalanges, differentiating it from the hand of the acromegalic in Fig. 49. The proportions and size also serve as



differentiating factors. All epiphyseal lines are closed, although in some of the heads of the phalanges a faint epiphyseal line may be seen, suggesting delayed closure, with production of increase in length of the long bones.

#### CONCLUSIONS

(1) The general diagnostic information derived from the roentgenological comparison of endocrinopathic and normal subjects has led the writers to believe that the radiological signs offer encouraging prospects of being of more value than the basal metabolism, blood chemistry, and other so-called specific and laboratory determinations.

(2) Retardation of development of all the bones of the osseous system, not only of the carpals, in uncomplicated hypothyroidism can be demonstrated roentgenologically in all ages up to that of completion of normal skeletal growth. This will be an additional aid to diagnosis in those cases already beyond the age of normal carpal development upon which basis hitherto has depended the roentgen picture of osseous change indicative of hypothyroidism.

(3) Hypogonadism and eunuchoidism have consistently shown a definite late fusion of the epiphyseal ends of the long bones. While this has been suspected clinically, we are unacquainted with any definite roentgenological demonstration of these abnormalities in secondary hypogonadism. The late closure of the epiphyseal ends in the presence of an active hormone from the anterior lobe of the hypophysis explains the *overgrowth of the long bones* in these subjects.

(4) In anterior lobe pituitary insufficiency in which there is a primary deficiency of the anterior lobe and a secondary deficiency of the generative organs, there has been found uniformly present a late closure of the epiphyseal ends of the long bones, *associated with undergrowth* of these bones. The reason for the undergrowth of the long bones in the presence of the open epiphyseal ends in this disorder is the *absence of the hormone from the anterior lobe of the hypophysis*.

(5) In the pluriglandular syndrome, the development of the osseous system as demonstrated roentgenologically is very difficult to interpret. From the studies of our cases thus far, we are of the impression that the following facts obtain: (a) In

the thyro-pituitary disorder there is an advance of the carpal and long bone nuclei development over that of pure hypothyroidism unassociated with pituitary disorder. (b) In pituitary-thyroidism, there is a retardation of the appearance of the osseous nuclei, as well as of the fusion of the epiphyseal ends of the long bones, more marked than that in pure hypothyroidism or in the normal. (c) The markedly heterogeneous pictures presented in the multiglandular syndromes will depend upon the sequence in which the various disorders were superimposed upon each other. For this reason, the combination of the same glandular disorders might present entirely different radiographic pictures of the osseous development at the same age, depending upon the order in which the various glands might have become involved.

(6) In the less frequent but very instructive condition of *pubertas praecox* (suspected pinealism), the most unusual advancement in development of the bone nuclei and early fusion of the epiphyseal lines was found. The four cases studied confirmed our earlier belief relative to the effect of gonad hormone upon the osseous growth and development, and were a convincing confirmation of the exactly opposite picture consistently present in the hypogonad.

(7) Thymo-lymphatism in the few cases studied apparently presented much the same osseous retardation as mild hypothyroidism. The osseous development in positive cases of enlarged thymus should be more thoroughly studied, with the view of clearing up this much mooted point of the relation of thymus function to osseous development.

# AN ORIGINAL CLINICAL INTERPRETATION OF DERCUM'S DISEASE (ADIPOSIS DOLOROSA)

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Chair of Prof. Dr. M. R. Castex.

The so-called adiposis dolorosa or Dercum's disease has been considered by endocrinologists as a pluriglandular syndrome with predominant hypophyseal alterations. I shall try to show that this affection, like many others in which hypophyseal dysfunctions are said to be involved, must be considered as due to diencephalic disorders. For more details on the pathology of this region see my recent work on the hypophysis and diencephalon (1).

A noteworthy fact is the frequency of adiposis dolorosa or Dercum's disease in a diffuse or general form, especially in women, with distribution of fat similar to that in subjects with Frölich-Bartel's syndrome, which I think is its equivalent in the female sex.

In some cases, of Frölich's disease the fatty tissue aches spontaneously and when pressed upon as in Dercum's disease, and sometimes physical and psychical asthenia can be observed, with mental disorders, though the last are not always seen.

The extensive literature on this subject, in which disorder of the hypophysis is held to be the origin of the disturbance, is well known. I shall discuss, therefore, only the twelve autopsies of patients suffering from adiposis dolorosa, discussed by Lopez Albo (2), covering data up to December, 1920.

In six cases a serious alteration of the hypophysis was found. Dercum and MacCathy observed adenocarcinoma in one subject. Burr (3) observed a case in which glioma extended to the chiasma and to the fourth ventricle through the Sylvian aqueduct. Guillain and Alquier (4) noted a hypophysis hypertrophied to twice the normal size, with great augmentation of the connective tissue in the glandular part and alterations similar to a carcinoma. Inflammatory alteration was seen in two of Price's subjects (5); in one, the hypophysis structure resembled

an alveolar adenoma. Brüning (6) reported the case of a boy of ten years with adiposis dolorosa, during the last months of his life, on his cheeks, neck, chest and abdomen, with polydipsia, polyuria, glycosuria, convulsions, amaurosis and augmented development of the secondary sex characters; postmortem examination revealed an alveolar adenoma of the hypophysis. In a case reported by Dammann (7) the walls in Rathke's pouch were infiltrated. In a subject observed by Prunier (8) adiposis dolorosa was accompanied by symptoms such as epilepsy, blindness and imbecility, which seem to indicate that the disorder was of hypophyseal origin. (I do not think this interpretation exact, however.)

In three observations by Cushing of dystrophia adiposogenitalis, nodular lipomatosis appeared circumscribed in certain subcutaneous regions.

In addition to painful hypophyseal adiposity there is a painful form of acromegaly and it is universally believed that this is due to an hypophyseal adenoma of the anterior lobe.

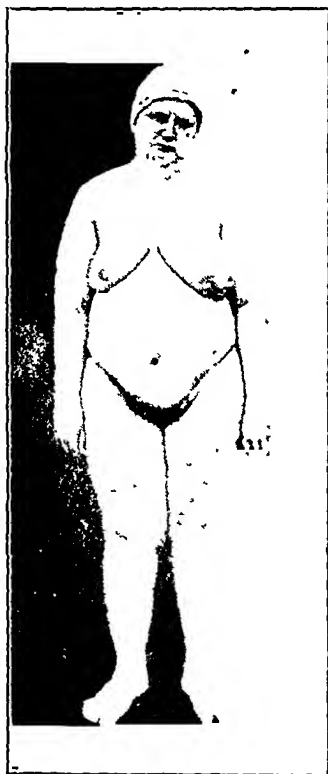
I admit that Dercum's syndrome is of pluriglandular origin in the majority of subjects, or at least a complex endocrine dysfunction (for instance, there may be a combination of thyroid, ovarian, adrenal or thymic or testicular disorder). I have particularly noted that the fundamental alteration has been attributed to the hypophysis, on account of its similarity to dystrophia adiposogenitalis which all the classic authors imputed to hypophyseal lesions, and it has not been thought that the cause of the first syndrome could be diencephalic alterations in the way accepted for Frölich-Bartel's syndrome.

After consideration of the numerous works, principally by Aschner (9), Leschke (10), etc., and the personal monographs to which I have referred, it would seem that Frölich-Bartel's syndrome is caused by diencephalic disorder and not by the posterior lobe of the hypophysis.

My theory is supported by many clinical and experimental data. In many cases mentioned in the literature and also in personal observations I have found that the pyramidal and the sensory tracts are frequently affected with symptoms similar to sensitive hemiplegia (Déjerine's syndrome) with participation of the optic thalamus which produces the symptom of pain.—a fact indicating involvement of the diencephalon. For details

concerning this point see Castellino and Pende (11). For this reason a series of anatomical and pathological studies of the diencephalon are required to prove unmistakably the existence of lesions of which the clinic warns us.

As I have said, in only six of the twelve autopsied cases of Dercum's disease has the hypophysis been found affected. The fact cannot be denied, but it also has to be established, that in any of those cases there were involved tumors which chiefly



1 and 2. Photographs showing distribution of fat in case reported.

had crowded the limits of the sella turcica, and, therefore, could either by compression or by metastasis impair the supra-adjacent diencephalic region. Other lesions, especially of arterial origin, should also be investigated, however, for instance, gummata, softening of organic tissues, meningitis, hydrocephalus of the third ventricle, etc., because in many of our subjects with Dercum's disease neither hypophyseal nor any other tumor clinically existed. Falta (12) also quoted a case of this kind.

Another argument in favor of this theory is its similarity to what has occurred in case of Parkinson's disease and certain choreas in which endocrine perturbations, especially of the parathyroid glands, were thought to be involved, but which after prolific recent investigations, are now attributed to affections of the central gray nuclei.

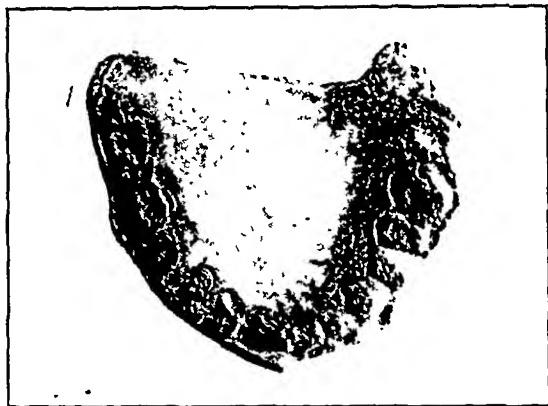
Recently, Roger and Aymes (13), repeating Livet, Nobecourt and Babonneix's observations, have reported four cases of transitory obesity with Parkinson's syndrome, tardy glyco-



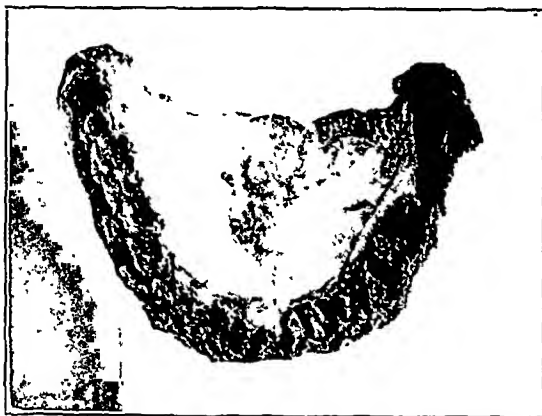
3. Photograph showing distribution of fat in case reported.

suria being noted in one subject. Considering the new interpretation of the adiposity in dystrophia adiposogenitalis and my own in Dercum's disease, the rapid obesity attributed to lesions of the diencephalon, that is, of the central gray nuclei and the basal zones of the diencephalon which are next to them, affected by epidemic encephalomyelitis, the observations of the above authors are explained.

The anatomical and pathological lesions which can be found in the diencephalon are easily changed from inflammatory processes, primary or consecutive, to lesions of the central gray nuclei, to primary and secondary tumors or compressions, prin-



4. Plaster cast of the superior maxillary.



5. Plaster cast of the inferior maxillary.

cipally tumors of the hypophysis or hydrocephalus of the medium ventricle or functional alterations or softenings due originally to arterial lesions of the region or to basal meningitis, especially syphilitic; the latter is frequently found.

#### SUMMARY OF CLINICAL HISTORY

The case is reported of a married patient twenty-seven years old, who presented a syndrome of painful general polysarcia with predominating hypophyseal distribution, asthenia, abulia, mental troubles and cardiovascular asthenia, marked by hyposystolia with benign nephro- or Dercum's disease. The patient had, moreover, extraordinary polyphagia at first, with considerable increase of fat, especially after childbirth; she weighed only 45 kilos at the age of twenty-two, but

had increased to 123 kilos at the time of examination. Pains appeared all over the body. Sometimes after she had had polydipsia and polyuria up to five liters of urine daily, the weight decreased to 108 kilos.

There was a heredo-syphilitic dystrophic terrain in full tertiarism and dynamism, characterized by many stigmata and a very early syphilitic angiosclerosis.

These symptoms were accompanied by a pluriglandular thyroid-parathyroid insufficiency, marked especially by the fact that the patient had not lost her milk teeth, which showed decalcification, all



G. Cranial skiagram of patient.

the teeth being reduced to the roots. There was pigmentation of adrenal type, dysmenorrhea and glycosuria with hyperglycemia of 44 mg. per 100 cc.

I diagnose this disorder as a syndrome of Dercum's obesity, glycosuria and polyuria, all of these symptoms being produced by disturbances in the centers of the diencephalon in consequence of circulatory, arterial lesions through precocious general angiosclerosis caused by late heredo-syphilis and cardiac-claudication in a benign nephrosclerosis.

The treatment consisted of dietary control with restriction of liquids, which was very painful to the patient, and antisiphilitic therapy (bicyanide of mercury and iodide).

As a result, the patient was cured. She lost 10 kilos in weight; the hyposystolia disappeared without cardiac tonics, the diuresis returned to normal and glycosuria disappeared.



## SUMMARY

From clinical observations, I believe the following to be the genesis of the main symptoms in Dercum's disease. (a) There is obesity resembling in distribution the hypophyseal type, as the result of perturbations in the trophic diencephalic centers, the picture resembling that of dystrophia adiposogenitalis. The pain in the fatty tissue is ascribed to lesions of the optic thalamus or to peripheral neuritis, since the pain is not necessarily constant in intensity and is sometimes observed even in genuine cases of Frölich-Bartel's disease. It is probable, too, that the thyroid and ovary later intervene in the production and maintenance of obesity, but as Dercum's disease it still is of frankly hypophyseal type. (b) The muscular and cardiovascular asthenia can be attributed to disturbances of the adrenals or the vegetative nervous system, central or peripheral. It is not uncommon to find this accompanied by mucous and cutaneous pigmentation; even the ovary can contribute to its production by an endocrine-sympathic mechanism. (c) The psychical disorders (not constant in Dercum's disease) can be attributed to toxic states of endocrine origin or to true encephalic lesions. The analogies between these factors are too well known to go further into detail here, especially since I have already previously done so in collaboration with Prof. Castex (14).

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# EXPERIMENTAL INVESTIGATIONS OF THE ROLE OF THE LEYDIG, SEMINIFEROUS AND SERTOLI CELLS AND EFFECTS OF TESTICULAR TRANSPLANTATION.\*

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The question as to the exact role played in the organism by the secretions emanating from the testicular structures is one upon which even at the present day there is no complete agreement among physiologists.

From the earliest times it has been believed that some direct co-relationship existed between the testicular fluids and the nervous mechanism of the brain and cord. Although it is manifest that psychic and nervous factors are concerned; that disturbances in the cortical centers affect the testicular secretions; and that disturbances in these secretions affect the individual psyche and character; yet we are still very much in the dark in regard to the exact mechanism which regulates such phenomena.

The earlier anatomists and physiologists understood that, apart from the generative function, the testicular secretions were concerned with the development and maintenance of masculinity in general; but it was not until toward the close of the XVIII Century that the subject began to receive any scientific attention. John Hunter (1) distinguished the secondary sexual characters as being quite independent of the reproductive act, and observed that castration prevented the development of these characteristics. The view generally held up to about this time was that the testicular secretion or sperm was a complex product elaborated from the blood in the generative organs, each of which added some vital quality to it. Whatever was characteristic in any individual, either sexual or personal, was considered to be due to some particular element in that individual's blood. Strict scientific investigation in regard to the evaluation of testicular products began with the experiments of Berthold of

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Göttingen (2), who was the first in 1849 to make autotransplantations of the testes of cocks into their abdominal cavities. Berthold found that in such transplantations the male characteristics were preserved in these animals and which he regarded as due to the blood passing through the vascularized graft.

In Berthold's work, and in the work of the many other investigators who followed him, a dual glandular function of testicular secretion is clearly recognized: not only was there the seminiferous output, but there was also something else which affected the whole organism and which was believed to be responsible for the production and maintenance of sex characters.

The point that has caused dispute in these later days, and which in the minds of some is not settled even at present, is not the question of a separate testicular secretion which influences sexual characters, but rather what particular part of the testicle was responsible for such secretion and how this secretion acted.

There are, in general, two broad views on the question at issue. There are those who maintain that the spermatogenetic portions of the testicular structures are alone concerned not only with spermatogenesis and elaboration and ejection of ripe spermatozoa, but that these same structures also prepare and discharge substances into the blood and lymphatics which act as a hormone and are directly responsible for secondary sex characters as well as for sexual desire and potency. There are others who say that the spermatogenous portions of the testicle are concerned only with spermatogenesis, and who attribute to the so-called interstitial cells, the Leydig cells, a distinct glandular function responsible for sex characters, desire and potency.

In considering the evidence submitted by investigators in support of the different views, on the basis of experiments made on the lower animals and the deductions drawn therefrom, we should be very careful in applying such to man, as the relationship between the testis and male sexual secondary characters differs much in the different orders and even in the different groups of the same order.

Leydig discovered the cells which bear his name in 1850 (3), and these interstitial cells were later shown to be of epithelial origin. The earlier investigators of these cells considered that they had the trophic functions of nourishing the seminiferous cells through the medium of the Sertoli cells. Others, however,

saw a different function for the interstitial cells which, according to them, elaborated a special internal secretion which was concerned with the secondary male sex characters, i. e., the special attributes physical and psychical, indicative of sex and distinct from the genital organs proper. The question as to the real function of these cells was apparently accepted as settled for the time being by the investigations of Ancel and Bouin (4), who, in 1904, showed that in mammals the interstitial cells form a true gland of internal secretion which alone exercised on the organism the function of determining male sex characters, libido and sexual potentiality, which function had hitherto been ascribed to the testicle as a whole. These authors also showed by their studies that neither the seminiferous structures nor the Sertoli nutritive elements of the testicle have any general action upon the organism, since neither show any phenomenon of compensatory hypertrophy, nor does their presence or absence make any difference on the showing of secondary sex characters in the organism, while the "interstitial gland" alone presented the phenomenon of compensatory hypertrophy, and that consequently to it alone was due the rôle of maintaining sex characters and sex instinct in the male. Bouin and Ancel's animal experiments showed further that when the interstitial cells were preserved, even if other cells were absent, the male characters persisted; and that, on the other hand, the loss of one meant the absence of the other.

Bouin and Ancel's conclusions were much strengthened by the more recent findings of Steinach (5) published in 1912. His experimental work showed that the sexual elements degenerated while the interstitial elements increased, and that sex puberty was dependent upon the secretion furnished by the Leydig cells, which he hence named the "puberty gland." Steinach's subsequent "rejuvenation" surgical work was based on the belief that the interstitial cells alone form the particular internal secretion governing sex characters and virility.

The experiments of Masaglia (6), Hanes and others corroborated the findings of Bouin and Ancel and further demonstrated that in the lower animals (roosters) the removal of atrophied testicles, in which, however, the interstitial cells were in good condition, caused in the adult a sudden loss of the principal secondary sex characters.

Since the ruling out of the sperm cells from the function of supplying a secretion responsible for the sex characters there has been some controversy as to whether the interstitial cell or the Sertoli cell supplied the organic hormone. General consensus of opinion has agreed, however, upon the finding that, while there is no evidence that the Sertoli cells elaborate an internal secretion, there is an abundance of facts to show that they act as nutritive cells to the sperm cells (Hanes). It should



Fig. 1. Human cryptorchid testis (transplanted into *macacus nemestrinus*). (1) Typical cryptorchid tubules. (2) Much hypertrophied interstitium.

be remarked, however, that Steinach and others leave the question open in regard to the participation of the Sertoli cells in the elaboration of hormone.

So far I have dealt only with those who favor the view that the interstitial cells alone form the gland of internal secretion in the testicle governing sex characters and virility. But this

interstitial gland internal secretion theory has not gone unchallenged. Among the recent investigators Voronoff and Retterer (7) rather deny the existence of an internal secretion affecting the sex characters being due to the interstitial cells, and attribute such effects entirely to the work of the seminiferous portions proper of the testicle. This view they have supported by a number of experimental investigations with histological findings both upon animals and the human subject.

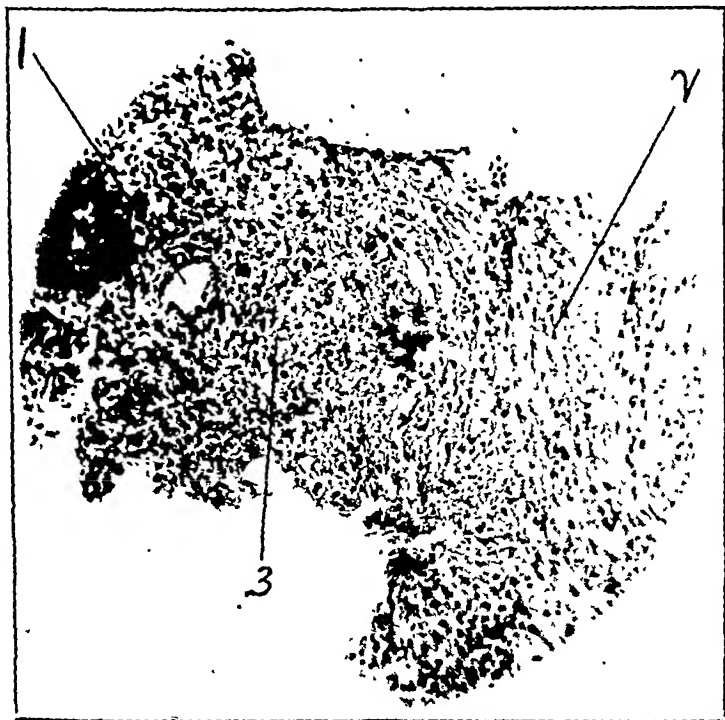


Fig. 2. Transplanted human cryptorchid testis into macacus nemestinus. Two months after transplantation. Magnified 240 X; ocular 7.5; objective S. Litz apochromatic. Hematoxylin and eosin. (1) Blood vessel. (2) Connective tissue and Leydig cells. (3) Same plus leucocytic infiltration.

Voronoff and Retterer and others find from their experimental work with testicular grafts that the epithelial cells of the seminiferous tubes become transformed into reticulated tissue and furnish a plasma, the absorption of which into the organism determines secondary sexual characters and desires. These observers reached the same conclusions from experimental liga-

ture and resection of the deferent canals and their conclusions are supported by Gley (8) and others.

Although the wealth of experimental work and observations in recent years seem not to have left the least doubt in regard to the interstitial cells of Leydig being the origin of the internal hormone governing sexual characters, desire and potency; yet, in view of the controversy which still exists on this matter, I have thought it desirable to make some further investigations tending to throw additional light on the matter. This experi-

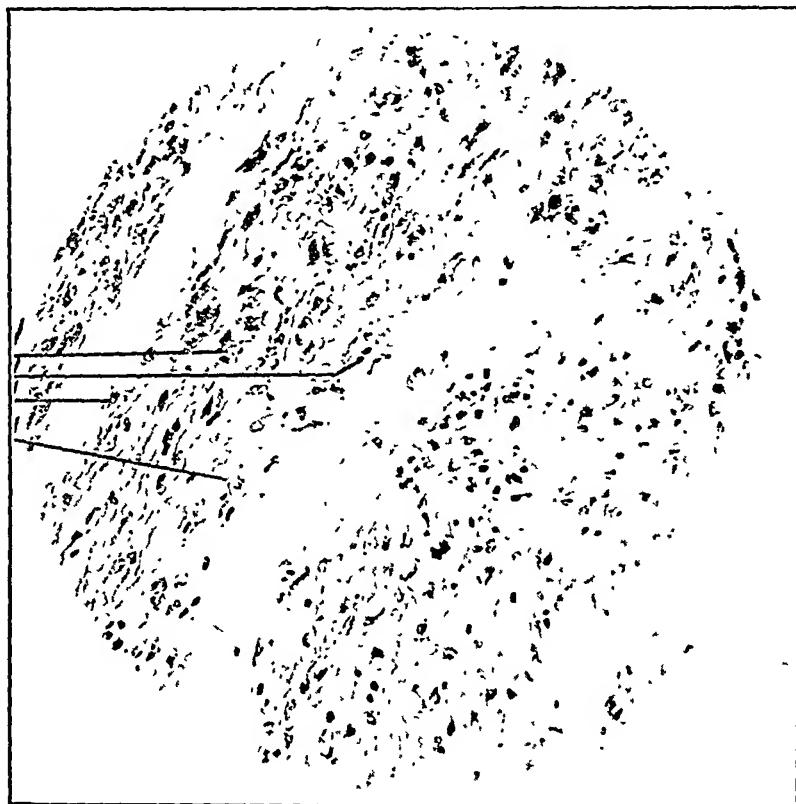


Fig. 3. Cryptorchid human testis after two months transplantation into *macacus nemestrinus* (1) Leydig cells. No tubules. No seminal elements.

mental work, which was done on the higher apes and on human subjects, will be described in succeeding paragraphs.

#### ANIMAL EXPERIMENTS

Six male apes (*cynocephali* and *macaci*) were selected for the research. They were at the age of full sexual maturity and very active sexually when placed with females of the same

species. They were all castrated. Gradually impotence set in and while a hyperstimulation of sex activity, as it were, ensued for the first two or three weeks after castration, the sexual ardor following the castration gradually declined so that about the end of four or five months all the animals were thoroughly sexually impotent and unable to react with an erection in the presence of females. Homotransplantations were then performed on five of the apes and a sixth had a cryptorchitic human testicle implanted into him. The testicles of similar animals were sub-

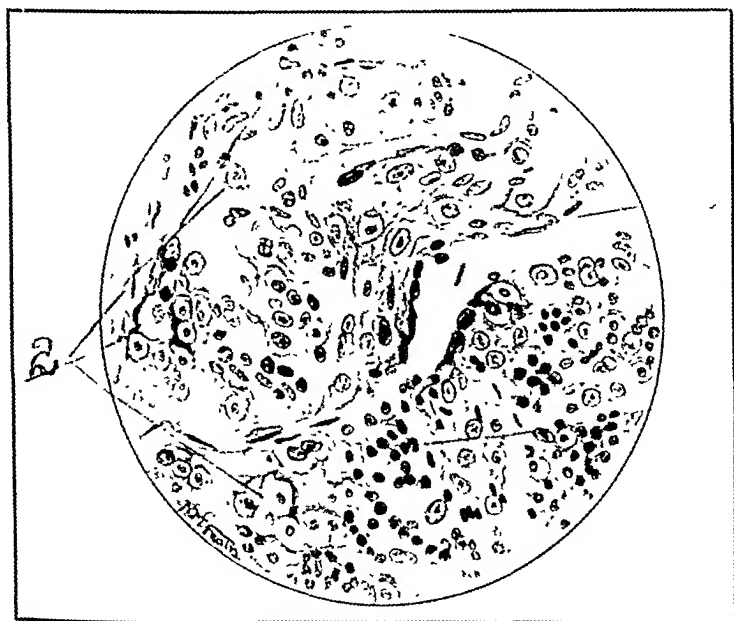


Fig. 4. Same as previous specimen. Drawn on larger scale. (1) Blood vessel. (2) Leydig cells. (3) Endothelial cells. (4) Leucocytes.

jected to the action of the x-ray sufficiently to destroy all seminiferous cells but not strong enough to devitalize the Leydig cells. Subsequent to the röntgenization of the testes removal of specimens from some for microscopic study has proved them to have become "interstitialomas" in the sense of Bolognesi and others (composed of interstitial cells alone). In this manner every element of doubt as to the absence of the spermatogenic cell has been eliminated. The roentgenized testes were then implanted into the castrated apes. Gradually these animals became potent and cohabited with females of the same species.



The cynocephalus in whom the cryptorchidic testis had been transplanted showed a reappearance of sexual ardor about six weeks after implantation. Removal from the cage in which the female was stationed into a cage where another male shared quarters with him caused his sexual ardor to become so great that very active pederasty was practiced between the two, the animal (male) carrying the transplant playing the active part and the other male a passive rôle.

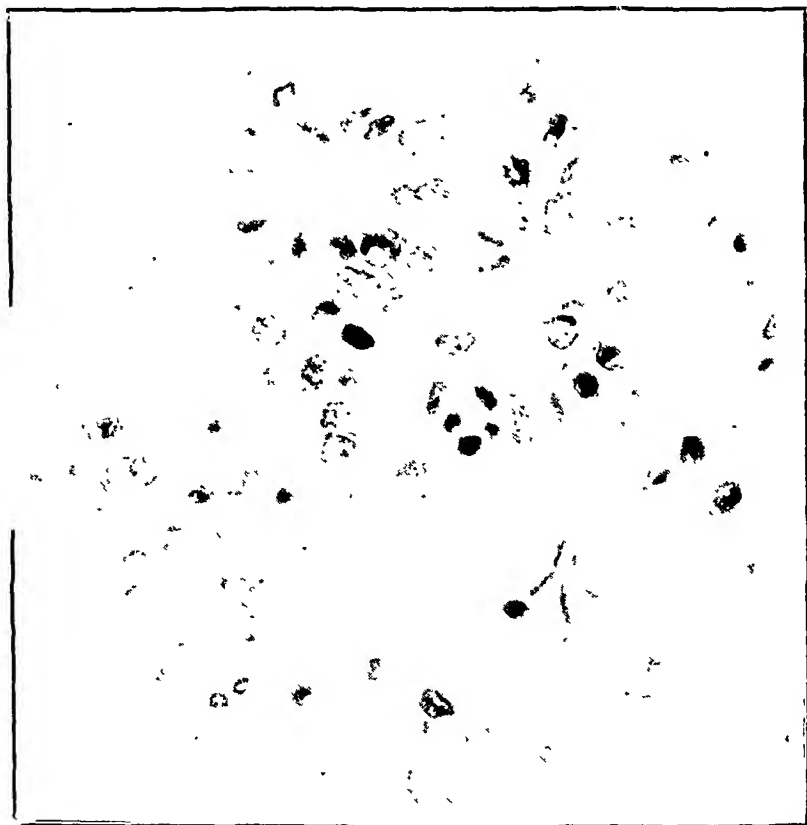


Fig. 5. Same as previous microphotograph magnified 768 diameters.

The cryptorchid testicle transplanted into monkey No. 6 (Cf. table) showed the characteristic cryptorchid picture (Fig. 1) with the well-known thickening of the seminiferous tubules, the disappearance of the characteristic contents and the extraordinarily hypertrophied interstitium.

A study of the cryptorchidic testis removed two months after its implantation showed the microscopic appearance de-

pieted in the accompanying five illustrations (Figs 2, 3, 4 and 5). The transplanted human testis into the macacus nemestrinus graphically illustrates and emphasizes the total absence of seminiferous structure and the substitution of Leydig cells and newly formed blood vessels in the implant, which was removed, as stated, after two months. Very few Sertoli cells were found and it stands to reason that the Leydig cells contributed to the intercretory function in these experiments and that the other elements may reasonably be excluded as having furnished any hormone whatever.

AUTHOR'S EXPERIMENTS TO ASCERTAIN FUNCTION OF TESTIS

Lab No Animal	Type of Animal	Date of Castration	Effects of Castration	Implantation*	Results
1	Macacus rhesus	Feb 10, 1921	Hyperstimulation gradual sexual de- cline Impotent by August, 1921	Feb. 1922 Homo- transplantation Testis of macacus nemestrinus	Gradual return of potency Normal sex activity April 1922
2	Macacus nemestrinus	Feb 10, 1921	Hyperstimulation gradual sexual de- cline Impotent by Oct., 1921	Feb. 1922 Homo- transplantation Cynocephalus	Potent June 1922 Potency uninter- rupted and con- tinuous
3	Cynocephalus	Feb 10, 1921	No hyperstimula- tion Gradual sexual decline Im- potent by June 1921 Marked loss of weight	Feb. 1922 Homo- transplantation Cynocephalus porcarius	Gained weight potent May 1922
4	Cynocephalus	Feb 10, 1921	Gradual sexual de- cline Impotent by Sept 1921 Ap- preciable loss of weight	Feb. 1922 Homo- transplantation macacus rhesus	Gained weight gradual return of potency viz Feb'y one year after implanta- tion Imperfect erections loss of libido
5	Macacus nemestrinus	Feb 10 1921	Hyperstimulation Impotent by Dec 1921	Feb. 1922 Trans- plant cynocephalus	Remains impotent April, 1923
6	Macacus nemestrinus	Feb 10 1921	Sudden impotence complete by Dec 1921	Feb., 1922 Hetero- transplant, crypt- orchid testis from human	Potent six weeks after implanta- tion violent ped- erasty with an- other monkey Died Jan 1923 in struggle with another monkey

\*The transplanted testes were converted into 'interstitialomas' by exposing them to the action of the x-rays prior to implantation

## ANALYSIS OF TABLE

These experiments show 66⅔ per cent. of successes (return of potency after hetero- and homotransplantations); 16⅓ per cent. failure (No. 5) and 16⅓ per cent. partial failure (No. 4). Or, expressed differently, of the homotransplants we had 75 per

cent. successes and 25 per cent. failures. The transplant from the cynocephalus to the macacus nemestrinus was a complete failure, while the heterotransplant of the cryptorchid testis from the human was a thorough success. Following castration 50 per cent. of the animals showed a transitory hyperstimulation of sexual activity, followed in a shorter or longer period by complete impotence.

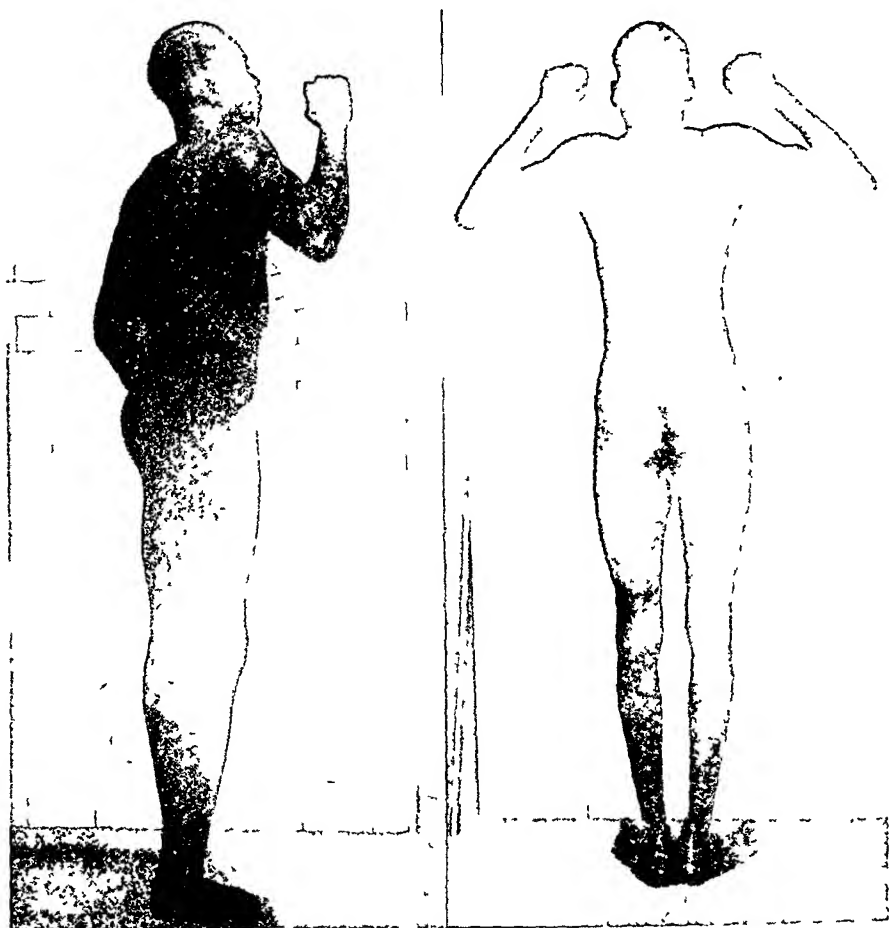


Fig 6 Showing lateral and posterior views of the patient. Note strong muscular development and absolute freedom from fat; perfect proportions and marked masculine habitus

#### EVIDENCE FROM HUMAN TESTIS

The following observations on the human subjects will, undoubtedly, throw some additional light on the questions at issue. Observation No. 1 concerns an individual, colored, a

porter by occupation. American, 23 years of age His family history is negative.

*Past History:* In 1906 the patient had pneumonia. In 1912 he developed mumps, which was followed by swelling of both testicles.

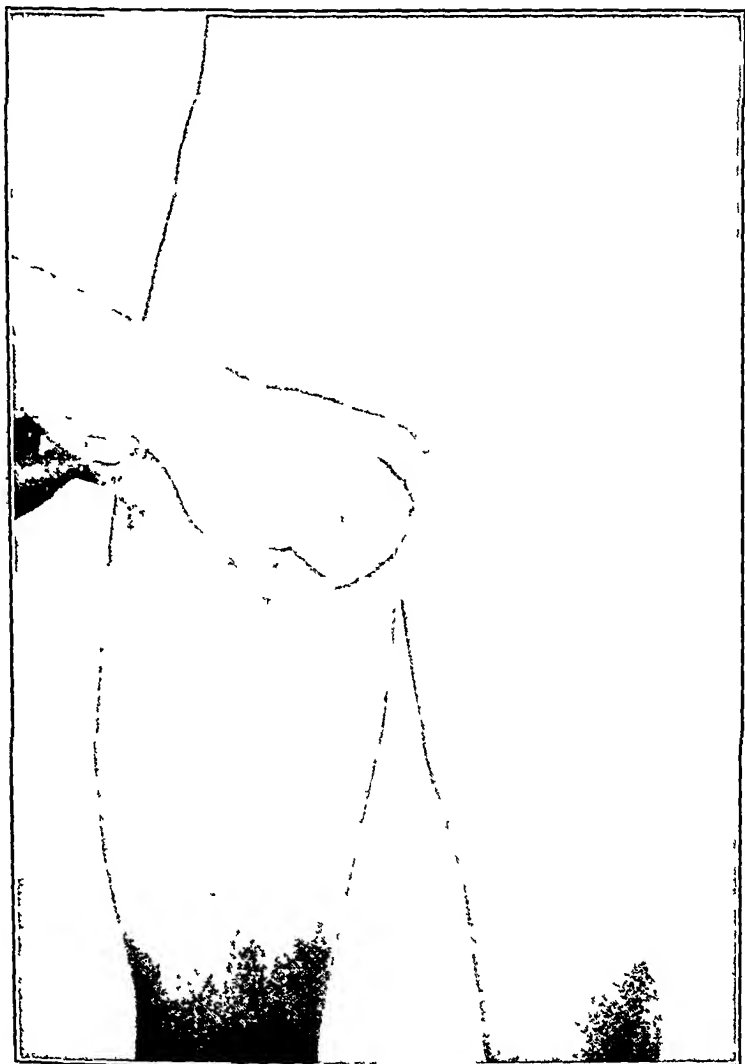


Fig 6 A Showing small size of testicles compared to height and general strong muscular development of the rest of the body

He remained in bed for sixteen days. His *vita sexualis* was normal, so far as he could determine. He cohabited normally from the age of 12 years and on. He married in 1919 and at that time he observed

that the sexual act lasted longer than usual. He gradually found that he could not succeed in inducing an orgasm. This condition became gradually worse and more pronounced until at the present time the patient is unable to produce an emission, no matter how hard he tries. The sexual act is sometimes greatly prolonged. In order to test himself the patient often prolongs the act of coition to a period of about two hours, when, weakened from the strenuous exertion, he has to desist and with penis still erect give up the attempt, as he expresses it, in despair. In other words, his *libido* is intact and his sex characteristics absolutely normal.

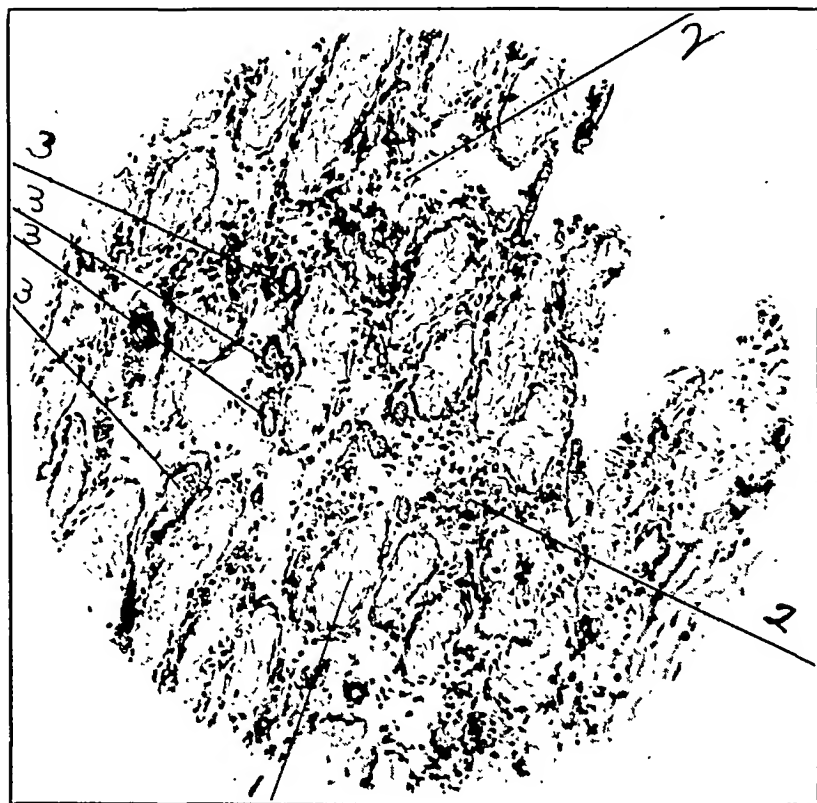


Fig. 7. (1) Tubuli seminiferi completely degenerated. No seminal cells. (2) Interstitium increased in quantity. Objective 7.5; ocular S (Leitz apochromatic). Magnified 205 diameters. Hematoxylin and eosin.

This being a case of great importance to the question at issue, the author decided to examine the testis of this man microscopically to ascertain the condition of the spermatogenic elements and also to study the cells of Leydig as well as those of Sertoli. The general appearance of the patient is that of a perfectly normal masculine individual, with testicles smaller in appearance than is normal for an individual of his size. This observation is corroborated by the statement of the patient that he had observed a gradual diminution in size of his scrotal contents, since he had the parotitis. We find no accumulation of fat, no effeminacy, no ear-marks of eunuchoidism. (Figs. 6 and 6-A.)

The patient was anesthetized with gas-oxygen, the *tunica vaginalis* opened and the testicles exposed to view. A thorough examination of the deferent ducts showed them to be normal; the epididymis was also normal but diminished in size. The consistency of the testicle was softer than is normally the case and much smaller than normal for an individual of his age and body dimensions. A section was removed for microscopic study. The gross appearance of the cut surface of the testicle was yellow, resembling closely in appearance a homo- or hetero-transplant. The specimen was fixed in formol and its microscopic study disclosed the following, Fig. 7.

The appearance on low magnification of the specimen stained with hematoxylin-eosin gives the appearance of a eunuchoid testis.

On higher magnification the findings were as follows: (Figs. 8, 8-A, 8-B and 8-C.) The seminiferous tubules are very much smaller

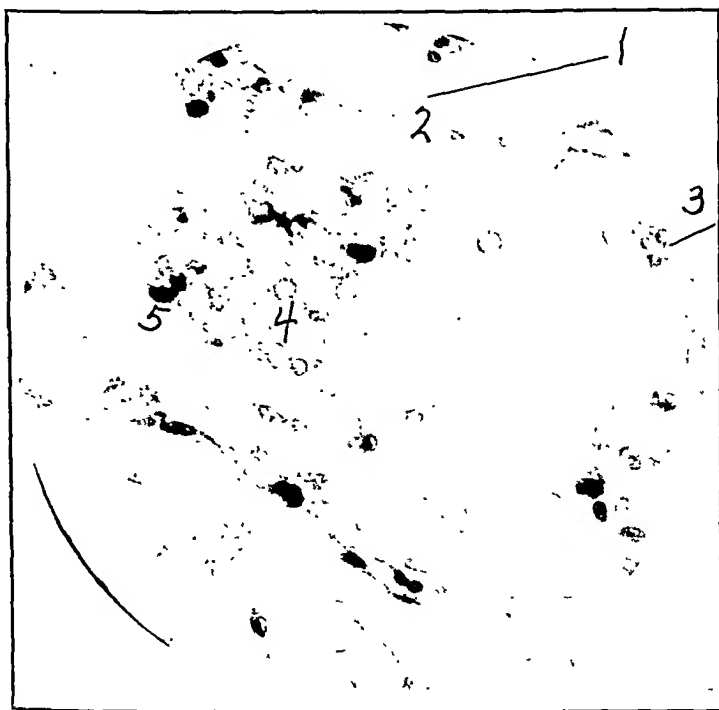


Fig. 8. (1) Tubulus seminiferus. (2) Wall of tubule composed of connective tissue. (3) Leydig cells. (4) Leydig cells. (5) Leydig cells. Objective 7.5; ocular 2. Leitz apochromatic. Hematoxylin and eosin stain.

than in the normal testes of a man of his age and their contents are completely degenerated. They are composed of a wall of very thin connective tissue. The lumen of the tubule contains a hyaline substance stained with the eosin. Not a single seminal cell is to be found upon studying a great many sections. In the interstitial spaces there is a great deal of infiltration with leukocytes. The vessels in the interstitium are numerous and filled with red blood corpuscles.

The tubules are widely separated from one another. The structure separating them consists of hypertrophic interstitium the main composition of which is chiefly lymphocytes, leukocytes, blood vessels and Leydig cells. The number of Leydig cells seems to be increased and their protoplasm is markedly granular. The nuclear wall is very strongly stained, sharply circumscribed and of normal size.

*Comment:* To the mind of the author the case recited herewith conclusively proves (basing his opinion on the clinical manifestations coupled with microscopical examinations) that neither the seminal cells nor the Sertoli cells have anything to do here with the produc-

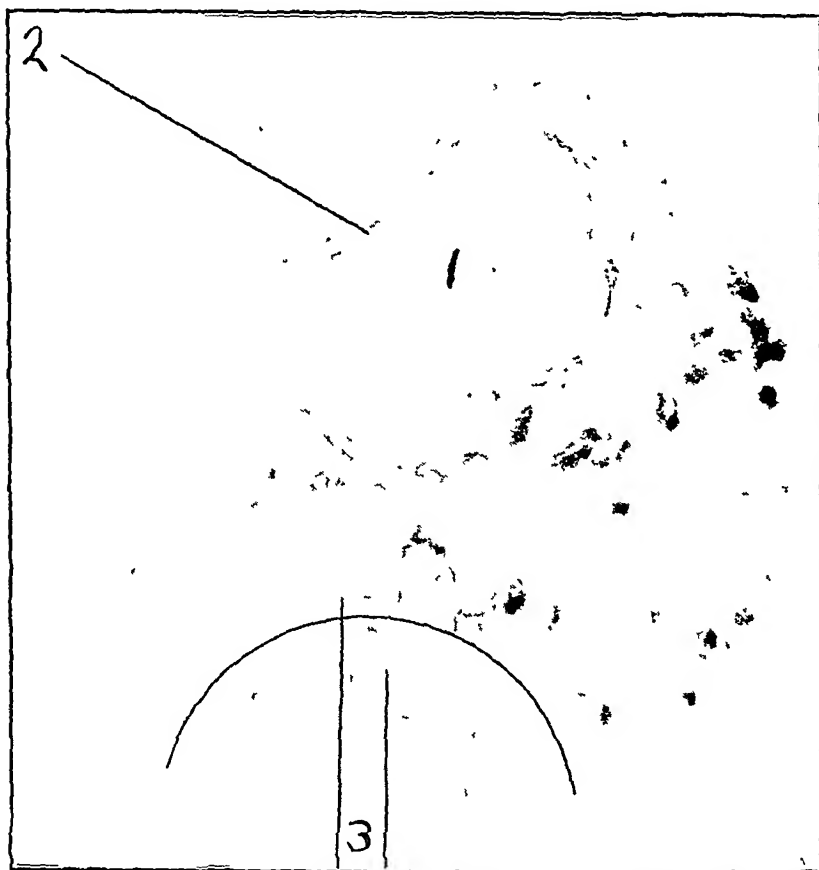


Fig S-A Testis of D W (1) Interior of seminiferous tubule. (2) Wall of tubule composed of a single layer of connective tissue cells. No Sertoli cells in any portion of the testis examined (3) Interstitial cells. Ocular S; objective 4. Leitz apochromatic. Hematoxylin and eosin. Magnification 511 X. Semi-circular area outlined shows in higher magnification in the following microphotographs

tion of *libido*, sex potency, and the retention of secondary sex characters. Not a single cell representing the lining of normal tubules nor an isolated Sertoli cell could be detected in studying a great many sections in the case recited. On the other hand, the Leydig cells were found to be increased in number and there was a good deal of leukocytic invasion in the field. For our intents and purposes the

question to be decided is, what causes, at least in the individual under discussion, the clinical manifestations enumerated above? Surely not the tubular elements, for they do not exist. The cerebral centers of the patient are certainly eroticized, as shown by the forceful and prolonged erections and the existence of marked *libido*: and, hand in hand with this we find the presence of an element in the sections studied and that is the Leydig cells. What other conclusion can be reached? None other than that the existing cellular elements are



Fig 8-B Testis of D W. Area outlined in previous microphotograph in higher magnification 764 diameter; objective 2, ocular 6 X Lertz apochromatic (1) Interior of tubule (2) Wall of tubule (3) Field containing Leydig cells (4) Another tubule containing leukocytes

responsible for the internal secretion and clinical manifestation so clearly manifest here. If we couple our findings in the last cited case with those related in the preceding group, in which by iont-genization the author was able to destroy all tubular elements and transplant pure interstitialomas into the bodies of previously castrated and impotent animals, in whom a return of *libido* and sex



potency became manifest, it accentuates and proves the premises set forth in this thesis in favor of the Leydig cells as the incretory apparatus for masculinization, erotization and sex potency.

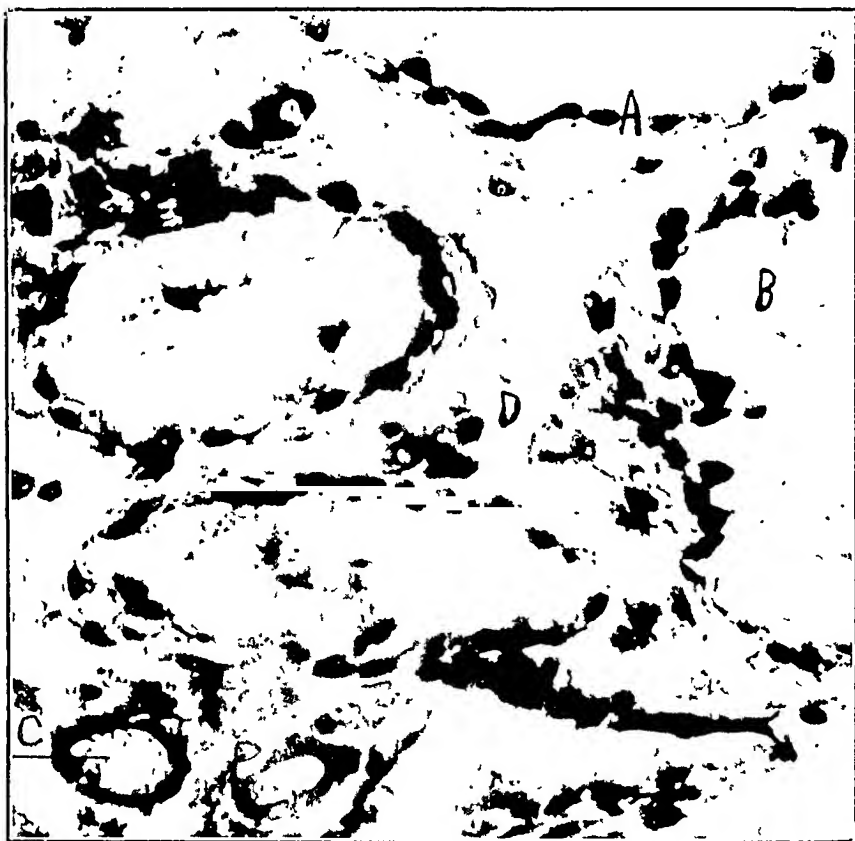


Fig. 8 C. D. W. Ocular 12 X; objective 2; 1536 diameters. (A) Wall of tubule. (B) Interior of tubule. (C) Blood vessels. (D) Interstitium containing Leydig cells.

**CASE II.** The following case will further tend to illustrate with even greater force the relative functions of the various component parts of the testis.

Mr. J. K., aged 70 years, was admitted to the American Hospital complaining of dragging and painful sensations in the lower part of the abdomen, particularly in the lower section of the inguinal region, on both sides.

*Family History:* Irrelevant.

*Previous Diseases:* The patient has always been in perfect health.

*Habits:* Used alcohol up until ten years ago, during which time he imbibed liquor to excess. Used tobacco all of his life, in moderation.

*Sexual History:* Patient arrived at sexual maturity at a rather early age. He masturbated occasionally. He had his first intercourse

when 15 years old, since which time he has been given occasionally to sexual excesses, cohabiting almost nightly. He has been married; divorced his wife, who has never been pregnant. His *vita sexualis* at the time of admission to the hospital, while not as active as in his younger days, is still very pronounced and he has sexual intercourse regularly once or twice weekly.



Fig 9. Gross appearance of calcified and degenerated intra-abdominal tumor (testis).

*Previous Operations:* Four years ago he was operated upon for the relief of a bilateral cryptorchidism. This operation, however, proved unsuccessful.

*Physical Examination:* The patient does not betray his age, looking more like a man in the late fifties than his real age. His hair is gray; mustache black; general nutrition and physical development normal. Wears an upper dental plate and has some bridge work in the lower section of the mouth. Chest well formed; expansion of the lungs normal. Thoracic organs negative. Blood pressure, systolic 190; diastolic 100. Examination of the abdomen discloses a soft rounded tumor at the site of the internal abdominal ring on each side. These masses are displacable upward but cannot be brought down-

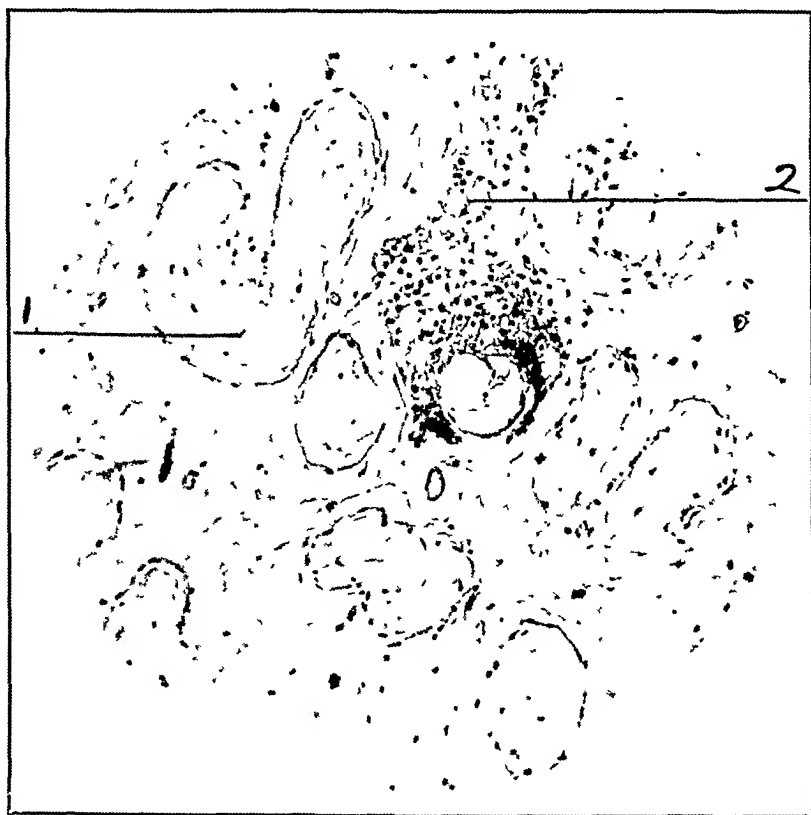


Fig 10. Mr J K Cryptorchidism Ocular S, objective 16 Magnified 105 diameters Leitz apochromatic Hardened in formolin, stained with hematoxylin and eosin (1) Empty tubuli seminiferi (2) Interstitial syncytium containing Leydig cells

ward. There is impulse on coughing on both sides. Palpation of the tumors, which in all probability are the testicles, is not painful. The examination of the urine shows a trace of albumin and many hyaline, fine and coarsely granular casts. Hemoglobin 80 per cent. Coagulation time of the blood four minutes. Blood Wassermann negative. Leukocytes 11,200 per c.mm. The patient is very anxious to be relieved of the dragging sensations and discomfort in the region of the incisions resulting from the previous operation and the frequently appearing "shooting" pains in that locality which makes him suffer to no small degree.

*Diagnosis:* Bilateral cryptorchidism; incipient bilateral inguinal hernia; neuralgia of the ilio-inguinal and iliohypogastric nerves, pos-

sibly due to scar tissue involvement resulting from previous operative procedure.

*Operation:* Under scopolamin-morphin anesthesia supplemented by gas oxygen, the patient was operated on the 29th of April, 1923, by the author.

*Operative Findings:* The exposure of the tumor through an inguino-abdominal incision on the right side disclosed it to be the testicle, which was converted into a necrotic mass of calcareo-sebaceous consistency, intimately adherent to the parietal peritoneum and contiguous structures. (Fig. 9.) This necrotic mass was ablated



Fig. 11. Mr. J. K. Cryptorchidism. Ocular 8; objective 8. Magnified 215 diameters; Leitz apochromatic. (1) Empty tubuli seminiferi. (2) Wall of tubuli composed of one layer of connective tissue cells. Total absence of spermatogenic elements. (3) Much thickness of blood vessel walls.

and found upon microscopic examination to consist of dead testicular tissue of degenerated and calcified debris. On the left side the exposure of the mass showed it to be a cryptorchitic testicle, which was freed from the surrounding structures and brought down to the scrotum after resorting to the operative technic the author is using in cases of undescended testes. Sections of the testes were submitted to microscopic examination.

*Postoperative Course:* After a fortnight the incisions were found to have healed *per primam* and the patient left the hospital.

*Microscopic Findings of Specimens from Testes:* The general appearance presented under low power magnification (Fig. 10) is

that of a cryptorchid testis. Close scrutiny of the picture shows that the seminiferous tubules were empty and their walls consisted of only a single layer of connective tissue cells. The spaces between the tubules are filled with islands of syncytium composed of Leydig cells surrounded by a vacuolar reticulum. Here and there blood vessels which are very much thickened are seen in the intertubular spaces.

Fig. 11 shows the tubules in high magnification. It displays to great advantage the thin unicellular connective tissue walls of the

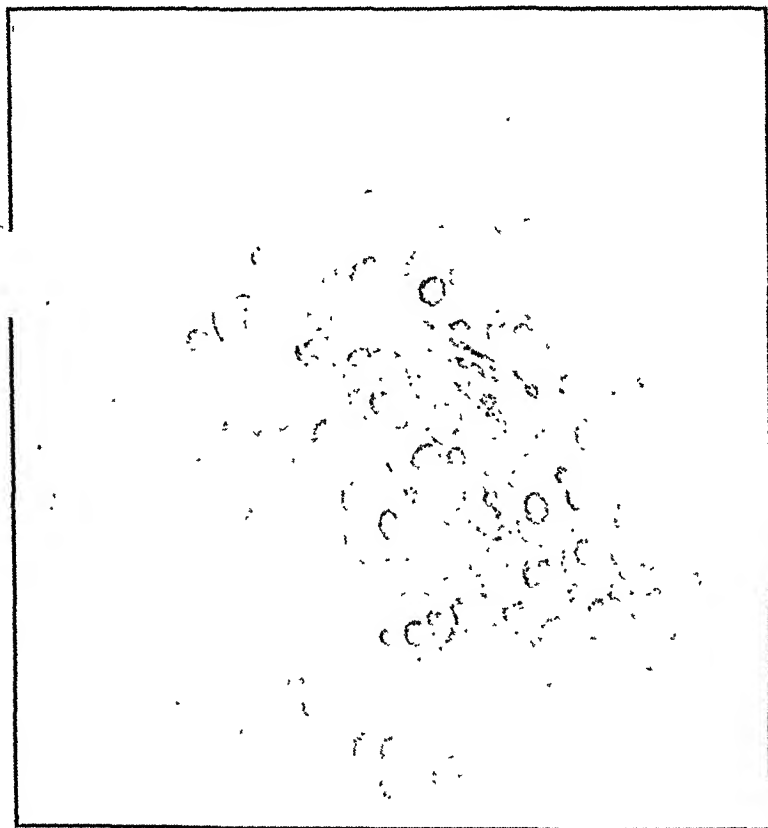


Fig 12. Mr J K. Cryptorchidism. Ocular 8; objective 4. Magnified 511 microns. Leitz apochromatic. Island of syncytium and Leydig cells between seminal tubules. Observe peripheral Leydig cells between the seminal tubules. Observe peripheral Leydig cells in act of apparent dissolution and their close relationship to reticulum.

tubules, the outlines of which are not regular but wavy. Here and there one meets, occasionally, a Sertoli cell.

Observing carefully Fig. 12, one sees a group of mono- and bi-nuclear Leydig cells with distinct outlines resting in a bed of reticulated syncytium. On the periphery of these islands of Leydig cells one can discern transformation of the outermost Leydig cells into the reticulated syncytium. The delicate reticular meshwork which contains the numerous vacuolated spaces is beautifully illustrated in Figs. 13 and 13-A. In some parts leukocytes are found in abundance. While normally the nuclei of Leydig cells stain a faint blue, some of the nuclei found here display a deeper color than usual.

Upon a close-up study of the Leydig cells themselves, shown in 13-B, the granular protoplasm of the cell bodies, their mono- and bi-nuclear structure is clearly depicted. In some of the spaces an epithelial cell is observed here and there, occasionally between the tubules.

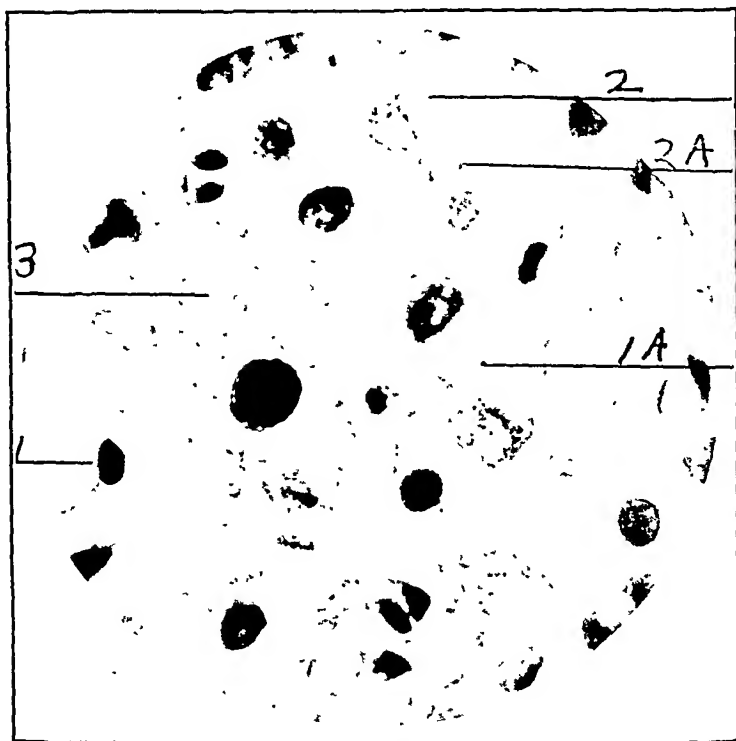


Fig. 13. Mr. J. K. Cryptorchidism. Ocular 8; objective 2. Magnification 965 diameters. Leitz apochromatic. High magnification of reticulum and hyaloplasm surrounding apparently active Leydig cells. (1 and 1-a) Vacuoles (2 and 2-a) Leydig cells. (3) Reticulum.

#### COMMENT

A critical study of this case brings the following facts vividly and emphatically before us: *First*, the total absence of spermatogenic elements in the tubules; *second*, the abundance of reticulated syncytium with well developed normal Leydig cells; *third*, the apparent transformation of Leydig cells into vacuolated syncytium; and, *fourth*, the persistence of marked sexual potency, normal secondary sex characters and remarkable virility in the patient. All these factors can lead to *one conclusion only*, and that is: the Leydig cells with their reticulated syncytium *alone* are, in this case, responsible for the clinical

manifestations and no increritory functions at all can possibly be ascribed to any other of the testicular elements.

Figs. 14 to 16 depict a eunuchoid patient of the author's whose feminine stigmata clearly indicates a lack of Leydig cell incretion. Microscopic examination of a section of the testis of this eunuchoid (Figs. 17 and 18) further emphasizes the imperative necessity of Leydig cell incretion for masculinization, development of secondary sex characters and cerebral erotization. In this case there is an apparent abundance of Sertoli cells and spermatogonia but no Leydig cells, and yet no masculinization



Fig. 13-A. Mr. J. K. Cryptorchidism. Ocular 12; objective 2. Magnification 1250 diameters. Leitz apochromatic. High power appearance of Leydig cells; observe granular protoplasm; binuclear cells, of which three are represented in the field, and one mononuclear Leydig cell.

was present, which speaks, also, against the internal secretory function of the Sertoli cells and spermatogonia.

It seems to the essayist that despite the views of those antagonistic to the belief in the increritory function of Leydig cells, to which group Kohn (9), Benda (10) and Stieve (11) recently have been added, his experimental work presented in this thesis, coupled with the excellent work recently done by

Lipschütz (12) of Dorpat, strongly points to the incretory function of the cells of Leydig, as stated above

Lipschütz has shown in a series of experiments that normal internal secretion of the testicle in mammals is not possible without fully developed interstitial cells. This is substantiated in my own experimental work, in which, however, Sertoli cells



Fig. 14 Eunuchoidism (Author's case) Observe characteristic appearance of face

were occasionally found and some cells resembling spermatogonia, but no other seminiferous elements (transplants, cryptorchids).





Fig. 15. Eunuchoidism. (Author's case.) Observe  
feminine type of breasts.



Fig. 16. Eunuchoidism. (Author's case.) Observe  
tendency to female form, adiposity and waist-line.

## METHODS

The technic used in the experiments and clinical studies herein reported has recently been described by the author before the Royal Academy of Medicine of Rome and the Surgical Society of Paris, France. This phase of the work has been published *in extenso* elsewhere (13) and (14). The following is a brief account of the most salient features.



Fig. 17. Eunuchoidism. (Author's observation.) Note absence of spermatogenesis and scantiness of interstitial tissue. Objective 7.5; ocular 16. Lertz apochromatic. Hematoxylin and eosin. Magnified 90 diameters.

In human implants the age of the donor is to be considered. He must have arrived at sexual maturity and be sexually normal from every point of view, preferably between the ages of nineteen and thirty-five. He must be free from syphilis, tuberculosis, malignancy, neoplasms, etc.

Human testes may be kept refrigerated anywhere from twenty-four to seventy-two hours and still be used for thera-

peutic implantation. The sooner they are implanted, however, the better. In the absence of human tissue the testes of the higher apes may be used (chimpanzee, cynocephalus). None of the other species show any blood relationship (precipitin test; Nuttall, Thorek) and if implanted are extruded, as are the testes of sheep, goats, rams and other lower vertebrates.

The site of implantation is important. Lichtenstern and others have failed to obtain good results because of the pressure

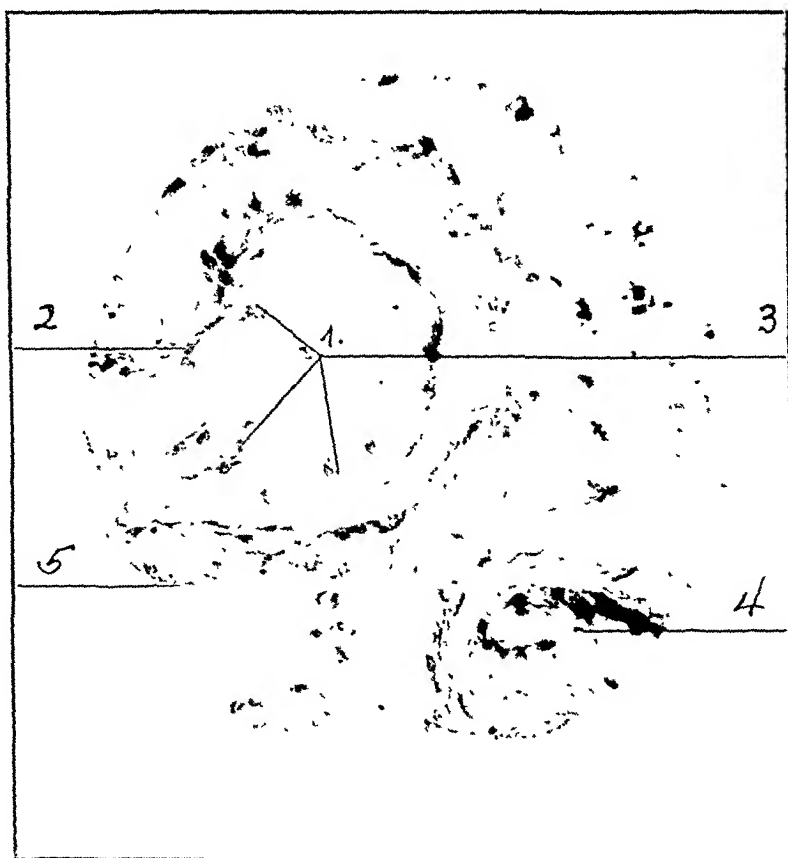


Fig 18. Lunuchoidism (Author's observation.) (1) Empty seminiferous tubule. (2) Wall of seminiferous tubule (3) Isolated spermatogonia. (4) Blood vessel (5) Connective tissue. Note absence of Leydig cells. Magnification of Fig 18 to 184 diameters. Lietz apochromatic microscope. Ocular 4 X; objective 16

to which the implant has been subjected. In the technic that I have evolved there are two spaces into which the implant may be placed without serious compression: in the supraperitoneal space in the region of the deep epigastric vessels (Technic No. 1) or in the retrorenal fossa between Gerota's capsule and the endo-

abdominal fascia (Technic No. 2). Pressure is effectively eliminated in either of these places.

As to the quantity of gland necessary for implantation, the technic advocated by Lespinasse has utterly failed in my hands. He uses 1 mm. or 2 mm. pieces of testis implanted in the rectus abdominis muscle. My experimental study supplemented by microscopic examination has revealed that implants treated according to the Lespinasse technic after two weeks were far

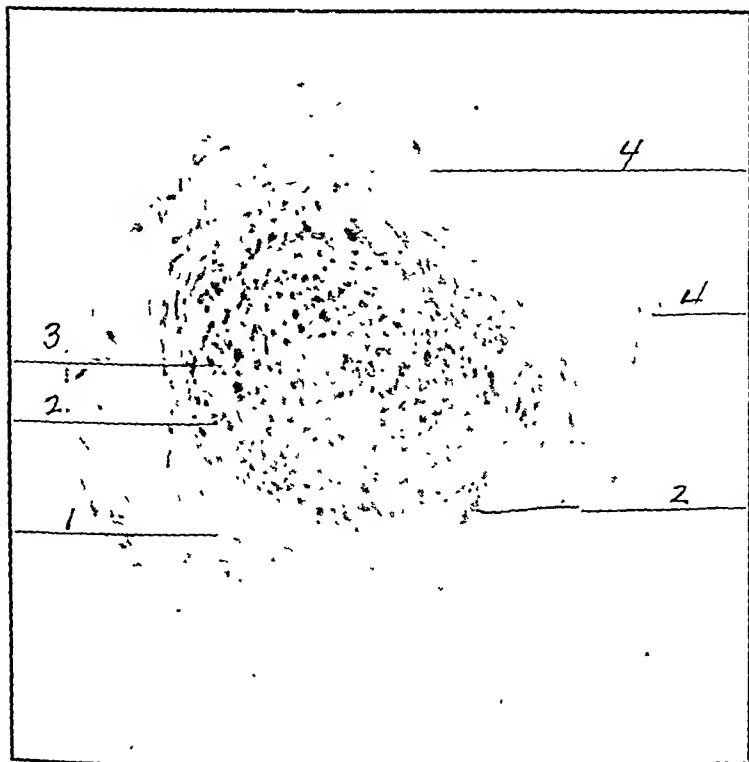


Fig. 19. Eunuchoidism. (Author's observation.) (1) Wall of seminiferous tubule. (2) Sertoli cells. (3) Spermatogonia. (4) Connective tissue. Note absence of Leydig cells. Magnification of Fig. 18 to 384 diameters. Lietz apo chromatic microscope. Ocular 4 X; objective 16.

advanced on their way to absorption and that in most of my cases at the end of the twenty-fourth day not a trace of the implant could be found. In some cases a very minute remnant could be discovered as late as the fourth week, but none thereafter. The parenchyma of the testicle when exposed to sur-

rounding structures is very early attacked by leukocytes, etc., and is absorbed.

#### CONCLUSIONS

From a review of the literature and from experimental studies with auto-, homo- and hetero-transplants carried on by the writer for the last number of years he draws the following conclusions:

1. The spermatogenic function of the mammalian testicle is limited to the tubules harboring the seminal cells.

2. The Leydig cells are alone responsible for the production of the internal secretion that gives rise to the secondary sex characters, sexual potency and cerebral eroticising products.

3. The spermatogenic cells do not seem to play any part in the formation of such internal secretion; the function of the Sertoli cells and spermatogonia may, however, play some rôle in this respect. This the essayist seriously doubts until more experimental proof is forthcoming.

4. The Sertoli cells seem to carry nutrition in the form of fat to supply the spermatogenic function of the tubules. The speaker is inclined to look at them as nutritional and storage cells only.

5. The essayist believes from his experimental studies herein recited and his hematological studies of the blood of the ape in relation to man that Darwin's concepts of the close biologic interrelation of the species under consideration are, in view of these findings, further substantiated.

6. The syncytial transformation of the transplanted male sex gland I believe to spring first from the seminal cells and after their disappearance from the Leydig cells, which are the most resistant of the testicular elements and are last to disappear in transplants.

Appended is a series of clinical results of ninety-seven testicular transplants observed over a period of four years, 1919 to 1923 (Cf. Table I and Table II).

In conclusion I wish to emphatically object to the term "rejuvenation." It is misleading, particularly to the laity who gain from such terminology the impression that by certain procedures the old can be made young. This is grossly erroneous! No organ or set of organs can be returned, by any method

thus far discovered, to a juvenile state when pathologic or advanced senile changes have made inroads on the structures and rendered them senile, in the accepted sense of the term. I

TABLE I.  
RESULTS OF 97 TESTICULAR TRANSPLANTS OBSERVED OVER A FOUR-YEAR PERIOD  
(1919-1923).

No. of Cases	Type of Cases	Type of Transplant	Results for Both Types of Transplants
69 (A)	SENILITY, physiological and pre-existing, some senile all due to terium and chronic constitutional diseases	29 homotransplants 10 heterotransplants.	31 symptomatic restoration to normal 13 markedly improved. 12 slightly improved. 13 failures
11 (B)	LOSS OF TESTES from trauma, tuberculosis, sarcoma or supuration of various types	3 homotransplants 8 heterotransplants.	8 markedly improved. 3 failures
8 (C)	NEURASTHENIA GRAVIS; sexual neurasthenia; impotency at early age not due to organic diseases	3 homotransplants. 5 heterotransplants.	5 markedly improved. 3 failures
5 (D)	DEMENTIA PRÆCOX 3. Other psychoses 2.	1 homotransplant. 4 heterotransplants	2 markedly improved 2 failures 1 slightly improved
4 (E)	GLANDULAR SYNDROME. Froehlich's disease 2. Eunuchoidism 1. Hypogonadism 1.	All heterotransplants	1 slightly improved 3 failures

TABLE II.  
RESULTS OF 97 TESTICULAR TRANSPLANTS OBSERVED OVER A FOUR-YEAR PERIOD  
(1919-1923).

RESULTS	GROUP A Senile Atrophy		GROUP B Trauma and Pathology		GROUP C Functional Disorders		GROUP D Psychoses		GROUP E Glandular Syndromes		TOTAL	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Complete symptomatic recovery	31	15.0	0	0	0	0.	0	0	0	0	31	32.0
Marked improvement.	13	18.8	8	72.7	5	62.5	2	40	1	25	29	20.0
Slight improvement	12	17.4	0	0	0	0	1	20	0	0	13	13.4
Failures	13	18.8	3	27.3	3	37.5	2	40	3	75	24	24.6
Total cases	69	100	11	100	8	100	5	100	4	100	97	100
TYPE OF TRANSPLANT												
Homo	29		3		3		1		0		36	
Hetero	40		8		5		4		4		61	

would suggest the substitution of the term "therapeutic gonadal implantation" in the place of the promiscuously used term "rejuvenation." The field of usefulness for such implantation

is varied and includes many conditions. Improvement in certain well defined pathologic states can be anticipated in properly selected cases following the use of proper material and the employment of proper technique. Undoubtedly further research and the accumulation of clinical data will place therapeutic gonadal implantation more firmly as a valuable addition to the armamentaria of the progressive physician.

Implanting the testis in its entirety causes a rapid regression because the tunica albuginea is very tough and not readily penetrated by capillaries. I, therefore, evolved a plan of destroying small parts of the tunica albuginea by means of the electric cautery, thus exposing the tunica vasculosa. The testis then becomes rapidly vascularized from the surrounding blood vessels. I call this procedure "lanternization" for want of a better term. The testis is then transplanted in its entirety.

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# THE ENDOCRINE ORGANS: A POINT OF VIEW

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The plea of Dr. August Hammar (1) for systematic quantitative statistical study of the endocrine organs for the determination of the normal range of variation and with particular reference to the body as a whole, was read by the writer with sympathetic interest. The importance of such investigational work is of course appreciated; laboratories might be mentioned in which just such growth statistical work is being emphasized. Such research is clearly of importance in the direct interpretation of endocrinological fact. It seems to me that there is another quite different aspect which these interesting structures present, and I venture, even though I am in no sense an endocrinologist, to call attention to it.

The general articles and addresses that have recently (2) appeared have stressed other more peculiarly clinical and physiological aspects, while the point of view I wish to emphasize, a biological embryological one, is therefore not included. For the ultimate understanding of these curious organs, however, must, I believe, be given due consideration.

Let me take as an illustration of my thesis the gonad<sup>3</sup> ovary and testis. Their influence on growth and metabolism is securely established through long recognized and reliable evidence, so that no question can be raised as to their endocrine significance, as may be done in the case of several structures and organs frequently included in the group. Not so securely established, but nevertheless quite generally accepted is the interpretation that the gonads are in fact "double organs"—in which the reproductive, germ-cell producing elements, are quite distinct, though intimately intermingled with a second gonadal constituent, an endocrine gland, the so-called interstitial gland. In many quarters and writings of distinguished biologists, the interstitial cells are accepted as unquestionably such specific gland cells. They indeed suggest gland cells in their large size,



abundant cytoplasm, and frequent granules usually (at least) demonstrable as free or masked lipid; whence the suggestion sometimes made that the active principle of the gonad is of such nature.

Without questioning for the present the correctness of this very general interpretation of these cells, it may be pointed out that even though it were shown that they were the source of the substances that determined the metabolic effect of the gonad, they would nevertheless remain unexplained.

Through the extended and consistent observations of a number of observers it has been well established that the interstitial cells are hypertrophied stroma cells, the characteristic connective tissue cells of the ovary and testis whose cytoplasm has become greatly increased and within which the distinct and characteristic granulations and lipid droplets above referred to have usually become demonstrable. These cytoplasmic constituents are, in many mammals, exceedingly abundant so that the cell-body appears as a mass of such droplets when these are preserved, and a vacuolar foam-work when, as under ordinary technique, the lipid is dissolved out. The centrosphere is likewise a striking feature of the interstitial cell—frequently of exaggerated or hypertrophied size. In other mammals these cytologic features are much less marked, particularly variable being the amount of obvious lipid present. Since, furthermore, particularly in the ovary, a transformation of the stromal cells of a more typical fibroblast type, to typical "interstitial" cells is continuously or periodically encountered, and there is also considerable evidence of a transformation in a reverse direction, it will be quite obvious that it is frequently difficult to determine whether a cell should be distinguished as an interstitial cell. This difficulty does not inhere to this cell type distinctively or in greater degree than in other instances in which one cell type is formed by progressive transformation out of another cell form. Instances might be cited in the blood cell series or elsewhere in which differentiation gradually produces structural change. The importance of determining the factors of such characteristic transformation of stroma cell to interstitial cell is so obvious that no discussion of its pertinence seems necessary.

Less generally conceded, perhaps, but to the writer quite as obvious would be the importance of ascertaining the condi-

tions determining the appearance of this cell type, even though it had been shown that they produced the substance or substances—hormones if you will—through which the gonads produced their effect on metabolism. To simply state that the “interstitial cells constitute a gland of internal secretion” or that “Nature has provided within the gonad an interstitial gland for the production of sex hormones” is insufficient, and leaves an element of mysticism that is unjustified. It might be stated that the “function” of clouds is to produce rain, but the present day physicist would scarcely consider it an adequate explanation of cloud formation. Jupiter Pluvius along with other mystic agencies no longer holds sway. Cloud formation is a phenomenon of nature outside the body, and while the application is confessedly somewhat remote, the comparison is not unjustified. Advance of science has progressively removed mystical agencies from dominion within the body as well. Determination of function can hardly take the place of an analysis of the underlying processes. Returning to the specific instance of the interstitial cells, it may be repeated that determination that they produce sex hormones would not do away with the determination of the conditions and causes underlying the transformation of stroma cell to interstitial cell. It is, of course, very important to determine the source as well as the nature of the substances emanating from the gonads, but if such come from stroma cells *after* they have undergone the transformation changes that make them interstitial cells, it would be at least probable that a knowledge of the conditions and causes underlying the change should have significance from the “functional” aspect as well.

The ovary and the testis express in their structure growth differentiations along divergent lines in accordance with the differences between the end-products—ova and spermatozoa—of what appears to be the same embryonic anlage. In the ovary the growth of the follicle and its fate—maturation and rupture or degeneration—are the phenomena of importance in seeking the conditions determining the appearance of the interstitial cells. In the development of the follicle the growth of the parenchyma (i. e., follicle cells and egg cells) is accompanied by a growth or rearrangement of the stroma of increasing distinctness to constitute the theca folliculi. While in smaller follicles

the distinction is usually not evident, in larger follicles in most mammals the customary division into a theca interna, cell-rich and vascular, and a theca externa, fibrous, with fewer cells, may readily be determined. During the growth of the follicle the theca cells are characteristic stroma cells, spindle-shaped with scanty cytoplasm. In the larger follicles, in the cat at least, cells are frequently seen that are taking on the character of interstitial cells, and at maturation (pig, Corner) marked change of this nature in the theca interna has been noted. It is pre-eminently in the collapse of follicles undergoing atresia that the theca interna cells enlarge so conspicuously and become recognizable as interstitial cells.

Numerous investigations (3) indicate the universality of the change in the degeneration of follicles, but it is equally evident that great variability characterizes the picture in different mammals. In the rabbit the ovary is a mass of typical interstitial cells, derived however from the theca of atretic follicles; in other forms so slight is the change and so obviously fleeting the condition that interstitial cells are regarded as absent. They may appear in some mammals some time before birth (cat) or again only with the onset of sexual maturity (rabbit). Taxonomic relationship has no significance here, as may be seen in comparing the ovary of rabbit and of guinea-pig. The interstitial cells may be bulging with lipid droplets (cat) or show no free lipid (pig) and this is apparently a characteristic of the species.

Whether distinct as a cell form or poorly defined to the vanishing point, charged with or free from lipid, formed early or late, the interstitial cells, at least in the vast majority of instances, are developments from the stromal cells of the theca interna of follicles undergoing the characteristic degeneration of atresia. It is clear, therefore, that in the altered stroma-parenchyma relations attending the degeneration of egg cell and follicle cell in the collapse of the follicle are to be found the conditions determining the change. Three possibilities at once suggest themselves: (a) the alteration in the vascular and nutritive relations accompanying the collapse of the follicle, (b) alteration in the nutritive relations following the cessation of follicular metabolism, and (c) the more or less complete cessation of the growth tensions under which the stroma had existed during follicular growth. As far as I am aware, no adequate analysis has

been made. From the quite evident interdependence of stroma (mesenchyme) and parenchyme (epithelium) in the growth of other organs, the writer inclines toward the last possibility, although the vascular element in the complex, here as elsewhere, is doubtless an important factor.

If in the ovary analysis is difficult, in the testis it is much more so. In the ovary the growth of the follicles comes late and furnishes unitary pictures; the differential development of the testis begins early, and as a whole. There is not only a growth of the complex of seminiferous tubules, but a curious intratubular growth. Interstitial cells presumably in all the higher mammals appear early. There clearly prevails the same specific differences as to amount of lipid content as in the ovary, and certain variations as to the amount, distribution and size of interstitial cells; but in general the conditions seem strikingly uniform—like the growth of the seminiferous tubules. The interstitial cells of the testis, like those of the ovary, are conceded to be modified stroma cells.

No attempt has been made as far as I know to analyze in the mammalian testis the conditions underlying the appearance of the interstitial cells. There is available, however, much circumstantial evidence indicating that there exists a reciprocal balance, parenchyma—stroma interrelationship, of such a nature that decrease in the seminiferous tubule is attended by increase in the interstitial cells, and *vice-versa*. There are a number of well established conditions in which this is revealed: (a) animals with a markedly seasonal breeding cycle (mole, woodchuck) show in the post-reproductive period a marked hypertrophy of the interstitial cells accompanying a corresponding decrease in the caliber of the seminiferous tubules with a suspension of spermatogenesis; (b) a number of infections, intoxications and other depressive abnormal conditions occasion frequently a diminution in the tubules with a suspension of spermatogenesis, and a corresponding increase in the interstitial tissue; (c) cryptorchidism, whether congenital or experimental, gives quite the same picture; (d) vasectomy or ligation of the ductus deferens is usually attended by a cessation of spermatogenesis with an attendant decrease in the size of the tubule, and a corresponding increase in the interstitial cells. All of these conditions are well known and the literature presenting the detailed observations need not

be here reviewed (4). There is consistently found accompanying atretic regressive change in the seminiferous tubules the interstitial (stromal) cell hypertrophy which is so strikingly a feature of the ovarian atresia folliculi. In the ovary, however, the localization is sharper, due to the distribution in time and space of the oogenetic processes, as the growth and degeneration of the follicles; whereas in the mammalian testis the regressive effects above referred to as an accompaniment of interstitial cell hypertrophy are general and distributed uniformly throughout the complex of seminiferous tubules in which also all stages of spermatogenesis (during its activity) are in close proximity.

The analysis of testicular conditions is thus more difficult, the difficulty being increased by the insufficient knowledge of the early growth and differentiation of the organ. In the testis of the tailed amphibia, however, occurs a cephalo-caudal distribution of the spermatogenetic processes, giving a sharp regional separation of the stages of growth of the tubules (lobules) and of their degeneration after departure of the fully formed spermatozoa. Accompanying the collapse and degeneration of the tubules (lobules) as Humphrey (5) and Champy (6) have shown, there is a marked and typical hypertrophy of the stroma (connective tissue) cells whereby they gain all the characteristics of interstitial cells. Different salamanders show different degrees of collapse, since spermatogonial multiplication may maintain or early restore the lobule. The stromal cells, as would be expected, show correspondingly different degrees of change. The observations of Humphrey are important in the analysis of stromal-parenchymal relation in the gonad and the origin of the interstitial cells.

Of the three possible factors suggested above as determining the stroma cell hypertrophy, a choice is even more difficult in the testis than in the ovary. Humphrey inclined to the nutritive alteration as responsible. It would seem that alteration of growth tensions accompanying the collapse of the lobule cannot be excluded.

It has been emphasized in the preceding paragraphs that the primary problem in connection with the so-called interstitial cells of the ovary and testis is the ascertainment of the conditions under which the characteristic change of the stroma cell takes place. The evidence briefly reviewed indicates that an

alteration in metabolic or growth conditions underlies the change. The transformation of stroma cell to interstitial cell seems to express an altered parenchyma-stroma relation, the stromal hypertrophic change accompanying degeneration, regression or diminution in the parenchyma. A number of features of interstitial cell structure (frequent presence of two nuclei, giant centrospheres, accumulation of lipoid) suggests that in these cells the transformation is of a regressive nature. Put somewhat differently, the interstitial cell seems to express an alteration in growth and metabolic balance between parenchyma and stroma.

The other aspect of the interstitial cell problem may now be briefly considered. Whatever the factors and conditions that determine their appearance, it is entirely possible that they may give off to the organism specific hormonal substances which would justify the use of the term "interstitial gland" as applied to these cells collectively. However, the evidence, if critically examined will, I think, be found to be inadequate. Ancel and Bouin, who introduced the name of interstitial gland, and Steinach, through his experimental work, have largely determined the very general acceptance of the interstitial cells as endocrine gland cells. They are the only cells in the gonad that look like "gland" cells; they make their appearance early in the growth of the testis, at about the time of the onset of sexual differentiation, and thus meet the requirement of internally secreting cells. Marked and intimate relation to the blood or lymph vascular channels has been claimed for them. Because of the frequency with which lipoid is a marked constituent of cytoplasm, it has been argued that the active principle must be lipoidal or with lipoid as an element in its composition. Hypertrophy of interstitial cells following ligation of the ductus deferens has been described as accompanied by increase in endocrine effect. Cryptorchid animals, in which gonads the interstitial cells are relatively very abundant, possess normal or even exaggerated mating instincts. The evidence is on no side conclusive, and when it is considered in connection with the variability of the interstitial cells in different mammals in distinctness, cytoplasmic composition, abundance and time of appearance in the sexual cycle, together with the circumstantial nature of the evidence associating interstitial cell with bodily response as cause and effect, grave

doubts may be expressed as to the correctness of the conclusions so frequently drawn. The following facts should be appreciated: (a) the "active principles" of endocrine organs exist in so minute amounts in the blood that they have not in any instance been directly determined either there or in the cells that produce them. Epinephrin perhaps constitutes an exception. Certainly in the case of the gonads it holds true. (b) Minimal amounts of endocrine tissue are capable of producing full endocrine effects. This has been formulated as the "all-or-nothing" principle. (c) The interstitial cells are modified stroma cells. In no one of the ascertained endocrine organs is the stroma suspected of determining the endocrine effect, except in the gonad. Hesitancy should be felt in making them an exception. Much weight, therefore, attaches to the protest contained in Kohn's (7) recent critique of the interstitial gland hypothesis and to Steve's (8) adverse pronouncement. Aside from the fact that interstitial cells look like gland cells, failure to appreciate that the "indifferent" cells composing the tubules of the testis in the absence of any spermatogenetic process are nevertheless parenchyma and a possible source of substances of endocrine effect is responsible for the acceptance of the interstitial gland interpretation. As long as there is living, metabolizing, parenchyma it cannot be excluded as a source of the substances through which the gonad produces its bodily effects. As far as I can ascertain, in no instance has a gonadal effect been demonstrated in the absence of the parenchyma. A priori, the specific growth processes of the ovary and testis would be thought of as responsible for any general bodily effect that they possess. Possibly, though to my mind not probably, the interstitial cells through their metabolism might contribute, but not as interstitial cells, since the general stroma cell of which they are transformations cannot then be excluded. As I believe others have appreciated, there is frequently over-emphasis of the endocrine *gland* idea, and nowhere is this more evident than in the gonad.

A number of recent workers, appreciating the inadequacy of the interstitial gland and the puberty gland hypotheses, have turned to the Plato interpretation of the interstitial cells as contributing to the nutrition of the parenchyma. The conditions in the mammalian (reptilian or avian) testis are complex and not easily analyzable. In the ovary, however, and in the amphibian

testis, the evidence is adverse. In the tailed Amphibia, in which the progressive changes in the spermatogenesis are regionally quite separate from the regressive changes, Humphrey has shown that it is only in association with the latter, the degeneration of the indifferent parenchyma and the collapse of the tubule, that interstitial cells appear. His observations should once and for all time obviate this alluring interpretation of this peculiar cell-type.

The corpus luteum, as a growth of the follicular wall after rupture and escape of the egg cell, is a structure whose specific bodily effects are apparently fairly well ascertained. The best evidence strongly indicates that its characteristic cell type, the lutein cell, which is presumably the source of its active principles, is parenchymal in origin—a hyperplasia of the follicular epithelial cell.

In the foregoing portion of this paper, I have emphasized that in understanding bodily structures such as the endocrine organs two aspects present themselves for consideration, and I chose in illustration the problem of the interstitial cell of the reproductive organs. These two aspects—which should not be confused—are: (1) the determination of the processes responsible for the appearance of the organ or structure, and (2) what may be styled perhaps its adaptative significance for the organism as a whole, which we term its function. These two aspects confront the biologist in his attempts to understand any bodily structure, and are particularly pertinent in the case of those peculiar bodily structures designated as endocrine organs. In the ultimate understanding of these, not only the determination of the source, nature and effects (on bodily metabolism and growth) of specific substances formed as a result of their metabolism is essential, but also the analysis of the processes that determined their existence. In the case of certain obscure structures—such as, for example, the glomus coccygeum, which is now, I believe, being dropped from the list of endocrine organs because of lack of evidence, and the more complex glomus caroticum—the latter aspect, ascertainment of the developmental processes responsible for their existence, becomes markedly important if we are to gain an adequate comprehension of them. It is quite possible that they possess no specific adaptative significance, or function.



Likewise in the case of the thymus, that unique structure whose endocrine function is still debated or even doubted, the determination of the processes that underly the development is of paramount importance. Considered from the point of view here stressed, that of the actual growth processes, it may be described as an epithelial and then epitheloid growth completely transformed through invasion from the surrounding mesenchyme of cells of lymphocytic character, which proliferating particularly in the zone bordering the mesenchyme (connective tissue) produces the characteristic distinction of cortex and medulla. Continued growth accompanying the "lymphocytic reaction" produced the equally characteristic lobulation. The structure produced differs fundamentally from "lymphoid" or lymphatic tissue, from which it should be distinguished, and to Jolly (9) we owe full recognition of the significance of the distinction. He termed the thymus, together with certain other similar structures, most notably the tonsils, epithelio-lymphoid organs.

The epithelial growth which undergoes the characteristic thymus transformation comes from a region of peculiar interest to the embryologist—and to the endocrinologist as well, since it furnishes thyroid and parathyroid as well as thymus and palatine tonsils—the embryonic pharynx. The mechanics of growth underlying the transformation of the branchial to the postbranchial phase of development are complicated and need not be referred to here. In 1911 (10) I called attention to the fact that the epithelial growth which undergoes thymic transformation may owe its existence to its peculiar relation to the growth shiftings accompanying the descent of the heart, for which I employed the term, "growth eddy," since negative growth tensions were strongly indicated as present there. The thymus I thus spoke of as a non-adaptative growth and called attention to the significance that the experimental work of Leo Loeb (11) and of Murphy (12) on the lymphocyte reaction and the fate of epithelial grafts possessed for its interpretation. The growth is not alone responsible for the expansion but produces the remaining feature of thymic structure, the Hassall or thymic corpuscles, which are clearly developed out of the original epithelium. These peculiar structures, I believe, may best be thought of as expressions of interior growth in a confined space. The resem-

blance to the epithelial pearls from pathological epithelial growths is striking. Indeed, their agreement with pearls exists not only in the concentric arrangement of the cells but also in an apparent keratization which, curiously enough, they often show. Cystic corpuscles are frequent and are clearly due not exclusively to dissolution of the interior as the corpuscle increases in size.

Considering briefly the other side of the thymus problem, it may be said that, throughout, the structure of the thymus gives no suggestion of a glandular significance. Possibly toxins are produced as Uhlenhuth (13) recently maintained. It might indeed be expected that end products of the growth metabolism would have general bodily effects and that such marked degenerations as occur would produce toxic substances. Possibly, again, the lymphocytic reaction, invasion and proliferation that constitutes such a striking feature of thymus formation, may be correlated with the existence of such toxic end products. Hammar (14) has more recently sponsored the interpretation that the thymus has as its function the production of antitoxins, whose source, however, he traces not to the lymphocytes but to the cytotreticulum and the Hassall's corpuscles. Decision is perhaps premature, but the writer still considers that there is lacking conclusive evidence of any specific adaptative significance—possibly excepting its hematopoiesis.

The dual aspect of the problem, which the interstitial cells and the thymus presents to the histologist, exists also in the case of the other structures of endocrine or suspected endocrine significance. Thus, to take for illustration two important organs, the thyroid and hypophysis (pituitary body), the acceptance of thyroxin (or any other determinable chemical compound) as the active principle of the thyroid, and the full determination of its effect in no wise explains the characteristic structure of the organ. Its peculiar embryology and histology with the presence of the colloid remain to be accounted for. Similarly, the structure, position and relations of the hypophysis cannot be thus explained no matter how complete may be the information as to the effects through active principles of its metabolism upon bodily growth, or in other ways. It is not to be expected that all endocrinologists possess direct interest in what may perhaps be termed the biological aspect of the endocrine organs, but that it

exists should be appreciated, and in the ultimate analysis it must be taken into full account. It cannot be mere chance that the thyroid and the hypophysis bring about the bodily effects they do. Their physiological (and pathological) activities must be in some way a resultant of their origin, which has determined what they are. To accept as sufficient the apparent fact that the body is equipped with a system of important organs, more or less interrelated, through which the metabolic unity of the body is maintained, is perhaps a necessary or wise temporary limitation of the problem of endocrinology. With this dictum, however, is accepted also an element of mysticism, and from mysticism science, I take it, aims to free itself. In certain instances an appreciation of the dual aspect of the problem which the endocrine organs present becomes of quite direct importance for the interpretations of the endocrinologist, as I have attempted to illustrate particularly in the instance of the interstitial cells. Certain embryological aspects of the endocrine problem I have already commented on (15). In a paper (16) not yet printed the developmental significance of the hypophysis is touched on.

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A CASE REPORT OF THE CLINICAL FINDINGS AND  
THE RESULTS OBTAINED IN THE TREATMENT  
OF A SEVERE CASE OF DIABETES BY  
THE PROVEN ENDOCRINE SUB-  
STANCE, INSULIN

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Mr. P. H. M., San Francisco, Calif., was admitted Dec. 4, 1923. He was 39 years of age, married, white, and a carpenter by trade; weighed 115.2 pounds.

*Complaints.* There was severe diabetes with weakness, especially of the legs, of such a marked degree that he could not walk; polyphagia and loss of weight.

*Family and marital history and habits* are essentially negative.

*Past History.* The patient had measles and chicken-pox as a child, many colds and sore throats throughout his life, and a severe attack of influenza in 1919. He believes that his initial diabetic symptoms began in January, 1919, while in Alaska, but they were very mild in character and no physician was consulted. He returned to San Francisco in July, but did not consult a physician until the following October, when the above symptoms were marked and he had a heavy, drowsy feeling, with acetone, diacetic acid and 6 per cent of sugar in the urine. He was given a diet list and instructions to measure his food in tablespoonfuls. He continued to work and the diabetic symptoms disappeared, although he does not know whether he remained continually free from sugar.

In December 1920, the diabetic symptoms again became severe and he consulted Dr. Lovell Langstroth of San Francisco, who sent him to the University Hospital. There he was desugared by starvation in 24 hours. His diet was eventually built up to approximately 2000 calories and he was taught to care for his own diet and test his urine.

On October 17, 1922, he entered the Lane Hospital of San

Francisco under the care of Dr. Thomas Addis. His condition was then very critical. There was a marked acidosis associated with edema. Three days of absolute starvation failed to desugarize him. On October 28th, he was desugarized and freed from acetone and diacetic acid on a diet consisting of carbohydrate, 15 gms.; protein, 30 gms.; and fat, 40 gms.; giving 540 calories. He again showed sugar, 27.8 gms. in a 24-hour specimen, when the diet was increased to C. 50, P. 60, F 70, 1070 calories. Eventually, it was found that the maximum diet upon which he could remain continuously "sugar-free" and free from acidosis was C. 20, P. 35, F. 40, 580 calories. During his 47-day stay in the Lane Hospital, although he was kept continuously in bed, he lost in weight from 132 lbs. to 116.5 lbs.

He was then referred to this clinic by Dr. Addis, arriving here December 4, 1922. On admission, he was free from acidosis and only a trace, 0.15%, of sugar was found in the urine. Except for his extreme weakness and the general run down condition associated with diabetes of this degree of severity, the physical examination was essentially negative. At that time, our insulin supply was very limited and we were obliged to apportion it as carefully as possible to keep alive the many severe diabetic patients who sought admission at that time. He was given a diet consisting of C. 35, P. 38, F. 83, 1039 calories and sufficient insulin to maintain him "sugar free" on this diet.

The insulin used throughout the treatment of this case was that of our own experimental manufacture. It was evaluated in grams of sugar metabolizing power per cc. by the rabbit method and on carefully measured patients. Sufficient insulin was given daily to make up the difference between the patient's natural tolerance for sugar-formers and those of his diet. Five-eighths of the total daily dose was given hypodermically before breakfast and three-eighths before supper.

On December 25th, we had sufficient insulin to increase his diet to C. 45, P. 46, F. 118, 1426 calories and his tolerance, when estimated by diet plus insulin, amounted to 65 grams of sugar-formers or sufficient to carry a 1000 calorie diet. He had lost in weight by this time from 115.2 lbs. to 111.3 lbs., but this loss in weight was considered inconsequential because his edema had disappeared and was undoubtedly due to a loss of

water. As our insulin supply increased, we were able to add to his diet.

On April 1st, his diet consisted of C. 77, P. 65, F. 182, 2206 calories, with a diet "G" of 133 and an insulin "G" of 58, making his total, natural tolerance 75. His weight had increased to 126.3 lbs., his strength had gradually returned and he was leading a fairly active, hospital life.

On May 8, 1923, we were further able to increase his diet to C. 91, P. 79, F. 257, 2993 calories. His weight on this date was 130.4 lbs. On this adequate diet, he has steadily gained in weight and strength. He has left the hospital and is working at his trade.

On September 22, 1923, his diet consisted of C. 95, P. 92, F. 260, 3088 calories. He has gained in weight to 163 lbs., a gain 52.7 lbs. over his lowest weight; his musculature is hard; his natural tolerance has not materially increased, being still in the neighborhood of 75 grams.

Aside from an occasional trace of sugar in the urine during the adjustment of a new lot of insulin, he has remained continuously free from sugar and acidosis throughout the entire ten months of treatment. Since he left the hospital, June 21, 1923, he has managed his own diet and administered his insulin.

The final step in the treatment of this patient will be a reduction in the diet and insulin to his individual maintenance requirements. We will advise him to do this when he reaches the normal weight for his height and age which will be 172 lbs.

We have used this case as a typical illustration of the efficacy of a proven endocrine substance because in the beginning, in other institutions than our own, his case had been carefully measured and proved to be by the older methods of treatment necessarily fatal. His progress is typical of many other similar cases that we have had. The reader is referred to the *Journal of Metabolic Research*, June, 1923, Vol. 3, No. 6, for a detailed report of the methods followed and the results obtained in the first one hundred cases in this series.

## A CASE OF EUNUCHOIDISM WITH RESPONSE TO TESTICULAR IMPLANTATION\*

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A young man aged 18 years was referred to the Clinic because of finding, in the course of a life insurance examination, a systolic blood pressure of 170 and an "improper development."

His mother is very nervous and had had a "nervous breakdown," apparently a functional neurosis, before the patient's birth; she had had fainting attacks, though not recently. A sister, six years older than the patient, is subject to fainting spells and sick headaches. A maternal uncle practically never shaved.

The patient had diphtheria at the age of 9 years and red measles at the age of 12. There is nothing notable in his history until the age of 12; at this time he grew rapidly and states that he was 6 feet in height when 12 years old. At this age also he began having "sunstrokes," during which he is unconscious for a few seconds to a minute; he sometimes feels dizzy for a few minutes to an hour before the attack but is unable to ward off the spell with ammonia or similar things. The attacks came frequently and made it necessary for him to be out of school three or four weeks at a time; in the past two years the attacks have not been so numerous. He is quiet during and after the attack and experiences no after effects. He had "abdominal cramps" when 16 years old which lasted for four months.

His voice began to change at the age of 12 but is not yet fully changed. At the age of 16 he gained rapidly in weight, increasing from 150 to 210 pounds within three months. His school work was fair, being in the second year of high school at the age of 16 when he had to stop because of the abdominal cramps. He drinks 6 to 8 glasses of water a day and passes a moderate amount of urine. In the past five months he has

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\*I am indebted to Dr. Lisser, Chief of the Ductless Gland Clinic, Medical Department, University of California, for permission to use his notes on this case.

had about four formed stools a day. He first shaved at 16 years and has shaved only six or seven times.

At the time of our examination the patient presented a striking appearance; he was apathetic, rather sluggish in his mental and physical reactions, and showed little emotional activity; physically he was tall and obese with a feminine configuration. The patient was 189.5 cm. in height with a span of 185 cm.; the upper measurement was 91.5 cm., and the lower, 98 cm. His weight was 89.5 kg. There was practically no hair on his face; the scalp had a good growth of moderately fine hair; there was no hair on the body or in the axillae; the pubic hair was rather of the feminine type of distribution, though there were a few hairs extending up to the umbilicus. The mammae were somewhat overdeveloped, especially the left, and on this side there was a mass in the breast. The thyroid was palpable, soft and tender. The pulse rate was 80; the patient stated that it was usually 108 to 120. The blood pressure was unstable, varying from 128/82 to 150/95.

The external genitalia were fairly normal except that the right testicle and epididymis were smaller than normal; the prostatic and seminal vesicle secretion obtained on massage contained large clumps of leucocytes, occasionally lecithin, but no spermatozoa. (Report of Dr. M. B. Wesson.)

According to the Binet test the patient was of normal mental age. The x-ray plate of the sella turcica showed no definite abnormality. The sugar tolerance test gave a normal blood sugar curve. Blood count and urine findings were normal. The blood Wassermann was negative. Basal metabolism was 5.2 per cent above normal.

The patient's configuration and the history of *petit mal* type of attacks caused us to regard the case as probably one of dyspituitarism, and he was given anterior lobe pituitary (Armour); after being on this for two weeks he was given a Stanley implantation of fresh unextracted testicular substance, but continued taking the anterior lobe pituitary (15 grains a day). Ten days after the implantation he had lost 1 kg. in weight and was much less nervous—for the first time since he was 5 years old he had stopped biting his finger nails; his appearance was much improved and he showed more animation and seemed more alert. He reported a month and again two



months later, stating: "I am feeling wonderfully fine," "I have not felt so good in years." Within two and a half months after the implantation he had lost 7 kg. in weight and had shaved four times in the last month of this period, whereas he had not shaved more than seven or eight times previously; he noted more physical endurance.

The patient continued to lose weight and four months after the implantation had lost altogether 10 kg. At this time the pituitary preparation was discontinued in order to observe the result of a second testicular implantation. A month after this second treatment he reported that he was now shaving once a week and had no more dizzy spells. It is now over three months since the last implantation and during this time he has not had any medicine; the change in his appearance is striking—he looks more alert and active and decidedly less obese than at the time of beginning treatment. He takes a much more active interest in social and recreational affairs than formerly and says he "feels marvelous." He now occupies a responsible position and is actively at work.

There is little doubt but that this remarkable transformation in appearance and feeling is due to the testicular substance. It is not felt that the pituitary tablets had any part in the improvement, since their discontinuance produced no relapse.

# REPORT OF CASES FROM THE ENGELBACH CLINIC

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## PITUITARY HIBERNATION

Mr. A. F., aged thirty-five, was referred to us by Dr. W. A. Dew, Belleville, Ill.

The first observation was made in May, 1923, at which time the patient visited The Engelbach Clinic, complaining of the following symptoms: (1) somnolence; (2) insomnia; (3) increase in weight; (4) fatigability; (5) decrease and final total loss of libido and potency; (6) excitability; (7) edema of feet and legs; (8) occasional nycturia; and (9) hyperhidrosis. The duration of these symptoms, with the exception of the increase in weight, which has been gradually progressive for the past twenty years, was one year. At the age of twenty-three the patient weighed 160 lbs., and during the past twelve years he has increased in weight to 255 lbs. His general health had been excellent until an attack of influenza two years ago, since which time he has never fully regained strength. The other symptoms have come on within the last nine months. The somnolence, an outstanding symptom, is so marked that the patient is unable to perform his ordinary daily occupations, falling asleep without difficulty at any time during the day, frequently while driving an automobile. There is insomnia at night, however. In this time libido and potency had shown a definite decrease, disappearing completely five months before this original observation. Symptoms pointing to possible renal involvement, edema of the feet and legs and nocturnal urination, have been present for several months, but not to a severe degree.

*Past history.* There were the usual childhood diseases, but no sequelae. No definite relation between childhood infections and the gain in weight was established. *Personal and family history* were negative.

*Physical examination.* The general examination revealed a person of distinct pituitary makeup, with marked abdominal and mons and slight mammary adiposity (Fig. 1). Evidence of subdermal infiltration about the wrists and ankles, with a trace of edema of the ankles, supraclavicular and posterior cervical padding, and other physical signs of thyroid deficiency were noted. The regional examination re-

vealed nothing positive except a moderately palpable thyroid, without bruit or thrill.

*Laboratory examination.* The basal metabolism was plus 23%. The blood-sugar was 0.100% (sugar tolerance test was not obtainable, owing to inability of the patient to retain dextrose). The adrenalin and pituitrin reactions were negative. A twenty-four hour specimen of urine showed a heavy trace of albumin; microscopic examination was negative. Total non-protein nitrogen of the blood was 39 mgms. per 100 cc. (normal, 25-30 mgms.). The phenolsulphonephthalein functional kidney test gave 30% in two hours. The Wassermann test was negative. Erythrocyte and leucocyte counts were normal; the differential was normal.

*X-ray.* The sella turcica and thymus were normal.

*Diagnosis.* The case was diagnosed as (1) pituitary-thyroid insufficiency (pituitary hibernation); (2) moderate renal insufficiency (secondary to endocrine disturbance).

#### DISCUSSION

The diagnosis of pituitary-thyroid insufficiency, resulting in a state of pituitary hibernation, is based chiefly upon the history and physical examination. The pituitary insufficiency is assumed on the basis of the marked gain in weight, with typical pituitary distribution of the adiposity, loss of libido and potency, and fatigability. The thyroid insufficiency based upon the somnolence and insomnia, together with the physical signs of hypothyroidism—as subdermal infiltration, supraclavicular padding, etc. (A similar case was reported by Engelbach and Tierney in Tice's Practice of Medicine.) An

interesting point which should be stressed is the elevation of the basal metabolism, in spite of the obvious physical signs of hypothyroidism. This has been found to be not an infrequent accompaniment of combined pituitary-thyroid deficiency, in many cases a basal metabolic rate of plus 50 or 60% being seen. The rate alone is no guide to treatment, and we find in these cases not only that thyroid therapy relieves the deficiency as manifested by an improvement in the physical signs, but that there is also a decided decrease in the basal metabolic rate.

The renal signs in this case we have been inclined to attribute to the endocrine dysfunction. The urine, while showing a heavy trace of albumin, revealed no abnormal microscopic findings. There was a slight retention of blood nitrogen, together with decrease in the "phthalein" output. The blood pressure was moderately elevated, systolic 148, diastolic 108 (hardly sufficient to indicate the presence of true interstitial nephritis).

*Treatment.* It has been found that the cases of true pituitary hibernation or pituitary-thyroid deficiency respond rapidly

to combined therapy, consisting of pituitary and thyroid substances; whereas these cases react only partially to thyroid or pituitary treatment when these substances are given alone or one at a time. In this patient pituitary and thyroid substances were exhibited by the following method: (1) thyroid gland,  $\frac{1}{2}$  grain three times a day, gradually increased to tolerance; (2) pituitary substance, gr. 15 to 20 four times a day (after meals and at bedtime); (3) pituitrin 0, m. 15 hypodermically daily, increased m. 1 each dose to the intestinal reaction; this patient was unable to take more than m. 15 of pituitrin 0 a day; (4) antuitrin, 1 to 2 cc. hypodermically daily.

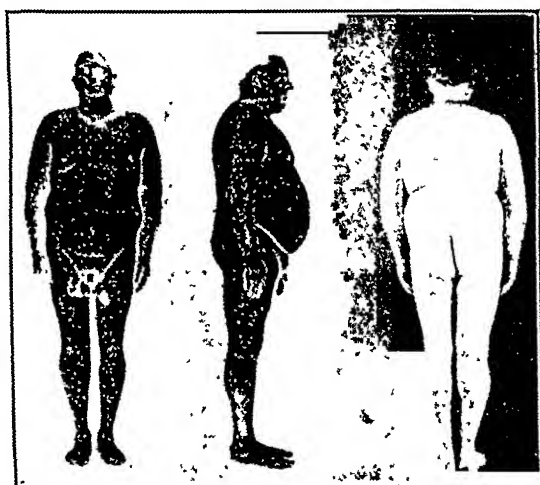


Fig. 1. Case of pituitary hibernation.

The second observation was made in September, 1923. The patient had remained under treatment for a period of three months and came in showing marked improvement in all symptoms. The original symptoms complained of, somnolence, insomnia, fatigability, loss of libido and potency, etc., had disappeared, so that he was able to remain at his work, with no evidence of somnolence and with normal sleep at night. Libido and potency had both returned, with manifest improvement in strength and general capacity. There was a loss of 30 lbs, in weight, together with disappearance of the urinary findings and edema of the feet and legs. At the present time he is taking 1 cc. of antuitrin daily, m. 15 of Pituitrin (0) daily, and gr. 2 of

thyroid three times a day. The basal metabolic rate at this examination was found to be plus 2.9%, demonstrating, as mentioned above, reduction of the basal metabolic rate under thyroid therapy.

Fig. 1 is inserted to show the physical type which is found constantly associated with the clinical picture of pituitary hibernation. In this particular case the loss of 30 lbs. in weight has not produced a change in the appearance sufficiently marked to warrant showing comparison plates. The clinical response, however, is definite. The circumference measurements to show important changes are as follows:

	May 31, 1923	Sept. 11, 1923
Neck, at thyroid cartilage.....	19 in. ( 48.3 cm.)	16 $\frac{3}{4}$ in. ( 42.5 cm.)
Insertion of deltoid.....	16 in. ( 40.5 cm.)	15 $\frac{1}{2}$ in. ( 39.2 cm.)
Thorax, at second rib.....	49 $\frac{1}{2}$ in. (126 cm.)	45 $\frac{1}{2}$ in. (115.7 cm.)
At ensiform.....	50 $\frac{1}{2}$ in. (128.5 cm.)	47 $\frac{1}{2}$ in. (120.7 cm.)
Abdomen, at umbilicus.....	55 $\frac{1}{4}$ in. (140.5 cm.)	49 in. (124.5 cm.)
At symphysis.....	53 in. (134.7 cm.)	44 in. (112 cm.)

### CONCLUSIONS

We have found the best results obtained in this type of case from intensive endocrine therapy as outlined above, combined pituitary and thyroid. We would stress again the reduction in the basal metabolic rate under thyroid therapy in these cases which show manifest physical signs of hypothyroidism.

### EUNUCHOIDISM WITH HYPOTHYROIDISM

Miss M. H., aged twenty-seven, was referred to us by Dr. S. B. Westlake, St. Louis.

This patient entered The Engelbach Clinic with the following complaints: (1) fatigability; (2) frontal and temporal headaches; (3) pain in the interscapular region and about the thorax; and (4) irregular menses. The duration of the complaint was about five months, with the exception of the irregular menses, which have been present since onset of the periods at fifteen. The flow was always moderate, lasting six to seven days, and never painful. The patient had no more than three consecutive periods at any time, and a history of amenorrhea of a duration of one to three months. Five months before entrance to the Clinic there was a menstrual period of nine weeks' duration, with moderately severe constitutional effects, malaise, weakness, loss of weight, etc. Following this the fatigability persisted, with the appearance in the last six weeks of

frontal and temporal headaches, coming on usually late in the afternoon, not relieved by correction of errors of refraction. With this in the past six weeks she has also complained of pain in the interscapular region and thorax, without other localizing symptoms. The last period occurred two months previous to entrance, was fourteen days in duration, moderate in amount, and not painful.

*Past history.* The general health was always excellent, aside from a history of recurrent attacks of tonsillitis. Growth in height was very rapid between the ages of twelve and fourteen. The patient was at that time taller than most children of the same age. *Personal history* was negative. *Family history.* Father had hemiplegia at this time. There was no positive history of other constitutional disturbances. There was a tendency to general increase in stature in the entire family.

*Physical examination.* The general examination revealed a female 5 ft. 5 $\frac{3}{4}$  in. in height, weighing 118 $\frac{3}{4}$  lbs. (normal weight for height and age, 135 lbs.). The measurements were decidedly eunuchoid, showing preponderance of the span over the height: upper (from symphysis to vertex), 30 $\frac{3}{4}$  in. (78 cm.); lower (symphysis to soles of feet), 35 in. (88.7 cm.); span, 69 in. (175.5 cm.). The regional examination revealed nothing positive. The systolic blood pressure was 100, the diastolic 70.

*Laboratory examinations.* Basal metabolism was minus 23%. Adrenalin and pituitrin reactions were negative. The blood was normal throughout, including Wassermann. The total non-protein nitrogen of the blood was 20.5 mgms. The functional kidney test, phenol-sulphonaphthalein, gave 60% in two hours. The urine showed a moderate trace of albumin, but was otherwise negative.

*X-ray.* Stereoscopic radiographs of the chest were negative.

*Diagnosis.* The case was diagnosed as a pluriglandular syndrome (eunuchoidism and hypothyroidism).

#### DISCUSSION

The diagnosis of eunuchoidism in this case is based upon the physical signs of the eunuchoid type, together with the history of menstrual disturbances indicating ovarian deficiency. Other significant points are the history of continued underweight, fatigability, general decrease in capacity, and local pains in the head and chest for which we were unable to find any other etiological factor. The basal metabolism of minus 23% establishes the thyroid deficiency in this case, although the physical signs of hypothyroidism were not in evidence.

*Treatment.* The indications in this case were for substitution of ovarian and thyroid substances, the patient receiving thyroid gland, gr.  $\frac{1}{2}$ , three times a day (gradually increased to gr.  $1\frac{1}{4}$ , three times a day), ovarian substance, gr. 10, four times a day (after meals and at bedtime), and ovarian substance, 1 cc..

hypodermically daily for one month, and 2 cc. daily for seven months. Within a month after institution of treatment there was a slight gain in weight, together with a general increase in physical capacity. The headaches improved and disappeared completely within a short time, with no return to this date. The pain in the chest likewise disappeared. There was, however, no change in the menstrual function. From the time of institution of treatment to August of 1922, at which time all medication was discontinued, the patient gained 14 lbs. in weight. Treatment, consisting of ovarian substance, without thyroid, was resumed in January of 1923. In the interval there had been a loss of weight of 7 lbs. and a return of the fatigability. The headaches were absent. The basal metabolic rate was found to be plus 0.5%. There had been, however, no marked change in the menstrual periods, except in the duration, which had decreased from seven to five days. The irregularity had not changed. The patient had not had in this time more than two consecutive periods. Medication was continued until March of 1923, with a gain in weight of about 7 lbs. and complete disappearance of fatigability. The last observation, in September of this year, revealed the patient in excellent physical condition, with the exception of slight evidence of fatigability. The weight has remained constant through the summer, and there has been no return of other symptoms.

#### REMARKS

The point to be particularly stressed in this case is the general improvement of the constitutional symptoms under ovarian substitution. In this case the thyroid element was not marked, although the patient showed an original basal metabolic rate of minus 23%. This, as mentioned above, did not correspond with the clinical or physical observations. We do not feel that the improvement was solely due to the thyroid, as might be claimed, for many cases of this type have been observed in which the basal metabolic rate has been normal and the ovarian substance has been the only therapy instituted, cases in which the response has been even more marked than in the above case. The failure of the periods to return to normal can be entirely accounted for, on the basis of failure of the gonads to be stimulated to complete function by the ovarian therapy.

# Editorial

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## THE EMERGENCY FUNCTION OF THE ADRENAL MEDULLA

Following the classical work of Oliver and Schafer on adrenal extract (1896) the efforts of physiologists for years were widely directed to attempts to explain adrenal function on the basis of adrenalin pharmacology. Since adrenal deficiency leads to low blood pressure and adrenalin administered by vein may result in striking increase in pressure, the theory that secreted adrenalin plays a major role in maintaining cardiovascular tonus seemed highly plausible and was widely accepted.

A critical consideration of the evidence accrued—especially that of the past fifteen years—seems to have rendered the “tonus theory” quite untenable. Furthermore, none of the pharmacological reactions other than cardiovascular seems to furnish a satisfactory basis for the explanation of adrenal function. Especially significant is Stewart and Rogoff’s observation that many animals survive in good health the removal of one adrenal and denervation of the other, operations which reduce the discharge of adrenalin below detectable limits. In view of the difficulties in applying pharmacological data some endocrinologists have gone to the extreme of suggesting that adrenalin plays no physiological role whatever, but represents merely an intermediate product elaborated as a step in some “detoxication” process, just as urea is elaborated in the liver.

A conception, however, that serves to harmonize many data was put forward by Cannon more than a decade ago. This is the well-known “emergency theory.” The theory initially was unusually well fortified by *a priori* considerations. The adrenal glands were known to receive sympathetic fibers, stimulation of which results in augmented adrenalin discharge. The sympathetic system in general was known to be markedly excited under conditions of emotional stress, pain and asphyxia, conditions characteristic of periods of emergency. The injection of



adrenalin into the blood stream was known to result in numerous reactions of obvious adaptive value in meeting emergencies. It would seem that the only way the theory could be greatly jeopardized would be to prove that the sympathetic fibers to the adrenal glands are anomalous structures that do not share in the activities of the rest of the sympathetic system. No convincing evidence that this is the case has ever been offered.

Plausible as the theory was, however, the task devolved upon its proponents of offering final positive proof of its correctness. This Cannon and his collaborators essayed to do by means of a crucial experiment. Through a flexible catheter introduced under local anesthesia into the femoral vein, blood was withdrawn from the vena cava anterior to the mouths of the lumbo-adrenal veins. Thus caval blood enriched by adrenalin from the glands could be secured. Cats were subjected to emotional excitation, to strong sensory stimulation, and to asphyxia. Blood secured during these conditions was compared with control blood taken prior to excitation. Assays by the well-known intestine method showed marked augmentation of adrenalin content during excitation. So clean cut and definite were the results that they seemed satisfactorily to establish the theory.

Stewart and his collaborators repeated the experiments, however, and obtained equivocal or negative results. These seem, curiously enough, to have been widely accepted as "disproving the emergency theory." Obviously they had and could have no such significance, but they did effectively challenge the adequacy of Cannon's method as a *crucial experiment*. Nevertheless, the method was well conceived and is, in the opinion of the writer, one of the best proposed for the study of the problem in question. It is, however, a method dependent upon only partially controlled "sampling" and the results obtained should be treated statistically to permit convincing deductions.

The modern conventional statistical methods of reaching reliable conclusions in the face of uncontrolled variables have been almost entirely neglected, however, not only in the investigations in question but in subsequent studies of the problem in Cannon's and other laboratories. Judging by his personal observations, there is little doubt in the mind of the writer that a high degree of correlation could readily be established between,

say, sensory stimulation and augmented adrenalin content of catheter specimens of caval blood.

After disposing of the foregoing observations to their satisfaction Stewart and Rogoff essayed in their turn to find a crucial method of studying the factors conditioning adrenal discharge. They adopted the "cava pocket" method. In this method blood from the adrenal veins is collected in an isolated venous pocket and subsequently assayed for adrenalin by use of intestinal segments. Its sponsors have insistently maintained that this is the best procedure available, despite the fact that it involves deep anesthesia and much trauma, which would seem to be important vitiating factors. But experience has shown that the method is capable of yielding significant data if subsequent adrenal stimulation is sufficiently marked. Using this technic Stewart and Rogoff have secured many negative results which have been adduced as controverting the positive findings in numerous investigations based on other methods, findings that in general support the "emergency theory." Despite the dialectic virtuosity with which they have been presented, however, negative results with the "cava pocket" are merely negative results and are valid only insofar as the method can be proved to be irreproachable.

Space is not available to review the extensive body of evidence supporting the "emergency theory" further than to call attention to an elaborate piece of work recently reported by Kodama from the Tohoku University in Japan.\* This investigator adopted the Stewart and Rogoff method in its entirety and studied the reflex effect of sensory stimulation on the adrenals in rabbits, cats and dogs. The results in the latter two animals afford the chief subject matter of the report cited. The data appear to be consistent among themselves and so definite as to leave no doubt of their validity. In thirty cats and dogs the output of adrenalin per minute was notably increased—often more than one hundred per cent—after stimulation of the central end of a cut nerve—usually the median. In only ten cases were ambiguous or negative results secured.

The controversy now would seem to be shifted from one as to methods to one of results in the use of a given method. The

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\* Kodama, S.: Effect of stimulation of the sensory nerves upon the rate of liberation of epinephrine from the suprarenal glands. *Tohoku J. Exper. Med.* (Sendai), 1923, 4, 166-242.

only suggestion offered by Kodama as to why Stewart and Rogoff failed to get positive results is that they used relatively too long periods in collecting the blood for assay.

In conclusion, the hope may be expressed that the controversy will be speedily terminated, as in all probability it readily can be, by supplementing existing data to whatever extent is necessary and subjecting these to rigid statistical analysis. Valid conclusions can thus be reached without accomplishing the very difficult feat of devising and carrying out an irreproachable crucial experiment.—R. G. H.

### IMPORTANT RECENT EXPERIMENTS ON THE HORMONE OF THE ANTERIOR HYPOPHYSIS

Ever since Pierre Marie astonished the medical profession by linking a peculiar osseous disturbance, acromegaly, with disease of the pituitary body, investigators the world over have directed researches in an effort to elucidate the functions of this interesting incretory gland. Its bilobar constitution materially complicated the problems that presented themselves. Considerable discussion ensued between internists, neurologists and neurosurgeons, between physiologists, anatomists and pathologists, as to what functions the anterior lobe controlled or influenced, as distinguished from the pars intermedia and posterior constituent. In 1901, Froelich described a syndrome, *dystrophia adiposogenitalis*, which he associated with an abnormal function of the pituitary gland. Cushing and others reproduced this clinical picture in dogs by partial hypophysectomy. The Levi-Lorain type of infantilism was soon ascribed to insufficient secretion of the anterior lobe. A rather common and characteristic "girdle obesity" was supposed to be dependent on posterior lobe deficiency. Classification of types of pituitary diseases were then made, probably the most elaborate being that of Engelbach and Tierney, where an earnest effort was made to assign special functions to the different portions of the hypophysis. In a broad way their views might be summarized, as considering the osseous abnormalities and secondary disturbances of gonad function (development of genitalia, secondary sex characters and menstrual function) consequent to abnormal anterior lobe secretion,

whereas the metabolic peculiarities (obesity, polyuria, glycosuria, etc.) are consequent to posterior lobe disease.

When a powerful smooth muscle stimulant was isolated from the posterior lobe (pituitrin—also known by other names), of great clinical value in obstetrics, in shock, etc., and when furthermore this substance was found to reduce the thirst and polyuria of diabetes insipidus in a remarkably specific manner, the latter syndrome became associated in many minds with disease of the pars intermedia and posterior lobe. But when Camus and Roussy, and Bailey and Bremer were able to reproduce diabetes insipidus and even dystrophy adiposogenitalis in dogs by producing lesions in the hypothalamus, more particularly the tuber cinereum, without any injury to the hypophysis, the whole subject of pituitary responsibility in these conditions had to be reconsidered.

In view of this confusion, it was all the more welcome that P. E. Smith's ingenious hypophysectomies in tadpoles resulted in such reliable and clean cut evidence. Fortunately in the tadpole the hypophysis is so situated that its removal or destruction could not possibly result in any direct injury to the hypothalamic area. These tadpoles did not metamorphose, because their thyroids could not develop normally in the absence of the hypophysis; they remained albinos, they grew slowly, and they became obese.

In the anatomical laboratories of the University of California, Evans has recently prepared extracts from the several lobes of the beef hypophysis. These extracts, freshly prepared and almost protein free, were administered intraperitoneally by Smith to his hypophysectomized tadpoles. This specific therapy entirely corrected the abnormalities alluded to above. The growth-controlling principle, and the hormone influencing the normal development of the thyroid, interrenal bodies and probably the gonads, was confined to the anterior lobe. The hormone correcting pigmentary upset was present in all three lobes, as was the principle which reduced the enlarged fat organ.

Those clinicians who have been convinced of an obesity of pituitary origin, difficult to reduce by diet or by the organ extracts at present available, will be especially interested to note that Smith was unable to reduce the large fat organ of his hypophysectomized tadpoles by either starvation or thyroid feed-

ing, but obtained complete specific response by intraperitoneal injection of the fresh pituitary extract just mentioned.

The climax to these carefully controlled and conclusive experiments came in the announcement by Evans and co-workers of unmistakable production of gigantism in rats by prolonged injection of anterior lobe substance. Thus finally we have the long awaited experimental proof that gigantism and acromegaly are due to an excessive secretion of the glandular portion of the hypophysis.

If this anterior lobe substance, when available, duplicates these remarkable results when tried in human beings, if it will stimulate skeletal growth in subjects of Lorain and Froehlich infantilism, produce normal development of genitalia and secondary sex characters, restore menstruation in post-adolescent amenorrhoea, and reduce girdle obesity, then there will have come to pass another epochal achievement in medical therapeutics, of the same brilliance as the discovery of insulin.

H. L.

## PATIENCE IN ORGANTHERAPY

Probably the most wondrous, consistent and convincing example of successful gland therapy is the veritable transformation produced in a patient suffering from outspoken myxedema by the administration of thyroid extract. If one seeks out the photographs of such an individual for a period of years prior to the establishment of the diagnosis, one will be able to discern the gradual deviations in features and body contours that mark the slow, insidious development of this malady. Non-surgical myxedema does not spring forth overnight, nor in a week, nor during a few months. Ordinarily it is a process of years. Thyroid extract is our most potent and reliable gland extract at present. This is generally conceded. Does its exhibition to a patient with pronounced myxedema cause immediate disappearance of signs and symptoms? Most certainly not. Ordinarily in a course of a week or two increased warmth is noticed by the patient, then gradually increased strength, more alertness, less lethargy. The metabolic rate is gradually elevated. Hair begins to grow after a few weeks, the excess fat slowly disappears, and many other

evidences of a return to thyroid normality appear from week to week. But the final consummation of a transformed individual, physically, mentally and emotionally, is not achieved for at least six months. The dose of thyroid extract or thyroxin is then finally determined which will preserve this restored individual in thyroid equilibrium—and let it be remembered, this dosage with occasional increase or decrease is thereafter administered for life. The patient's own thyroid is rarely restored to normal function, but the difference between the amount of secretion it can manufacture and the amount necessary to maintain normal function is fed to him in tablets or in capsules for many, many years. Acromegaly does not pop out in a few weeks; its development can be traced from previous photographs often over a span of five to ten years. Girdle obesity and menstrual irregularity culminating in amenorrhea do not appear quickly. A Froehlich's syndrome or Lorain infantilism does not present its text book picture inside of several years, nor does an Addison's disease.

Almost all pronounced, outspoken incretory disorders develop slowly, with the single occasional exception of a sudden fulminating attack of Grave's disease following shock. It should not be expected that specific gland administration will correct these abnormalities overnight. The unfortunately too common practice of prescribing a two weeks' supply of gland tablets or capsules, and expecting positive achievements within such very brief period, is quite absurd. It is beside the point that the adrenal, ovarian, pituitary and testicular products at present available are far from perfect in standardization or potency. Nothing can be expected from their haphazard administration, usually in inadequate dosage over a few weeks time. Not even thyroid extract will prove efficacious under such conditions.

Patience in organotherapy is absolutely essential. Many months of careful trial are necessary before failure must be admitted, and if beneficial results have been obtained, therapy must be long continued. Gland therapy for marked gland deficiency is rarely a cure. This is again perfectly illustrated by insulin. It is supplementary therapy, supplementing from the

outside artificially prepared hormone, to add to the deficient hormone prepared inside the patient. The casual prescription of a dozen or two gland tablets of whatever kind and for whatever condition is a waste of time and money. It accomplishes nothing, the patient is disappointed, the physician loses interest, and the science of endocrinology is unfairly condemned. Gland therapy should only be attempted where there is definite indication, and then its application should be continued with patient persistence until a fair judgment can be rendered after a fair trial.

H. L.

# Book Reviews

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THEORY UND PRAXIS DER STEINACHSCHEN OPERATION. Peter Schmidt, Vienna, 1922, Rikola. 90 p.

Schmidt is considered the foremost German exponent of the so-called "rejuvenation method" of the Austrian biologist. He first reviews Steinach's work from 1910 to 1920, in which evidence of the dependence of the secondary sex characters on the internal secretions of the generative gland was adduced. A list is given of the investigators who used Steinach's method on animals and on human beings, and their work is briefly described. In the conclusion of the theoretical part Schmidt discusses at length the Leydig cell theory, and clearly defines the point of view of Steinach and his school as compared to that of his opponents. In Schmidt's opinion the question is no longer "Has vasoligation an effect?" but "Why has vasoligation an effect?"

The question whether the generative portion of the testicle is the hormone producing tissue or whether this function is to be ascribed to the interstitial tissues is decided in favor of the latter theory after the pros and cons have been reviewed in a thorough and enlightening manner. It is concluded that the sex gland has a definite sex specific function; that the hormone production in the sex gland is independent of the production and discharge of procreative cells; that the gonadal hormones are of extreme importance for the formation and preservation of the physical and psychic sex characters; that transplantation, vasoligation or x-ray exposures produce an increase or a renewal of hormone production; and that increase of hormone production in persons aging partially, prematurely or at the physiological time causes rejuvenation. A citation of Bab ends the theoretical discussion: "We must avoid trying to do away, by discussion, with anything new that has been clearly demonstrated. In the end, facts will prove to be stronger than opinions."

In the practical part Schmidt begins with a brief review of the clinical experiences of Lichtenstern, the first to operate upon Steinach's patients in Vienna, citing in detail 3 of his cases. He then reports 24 cases of his own, laying special stress on the objective findings. He concludes that the results of his own observations and also those of others reveal a great number of changes that vasoligation has produced in the somatic as well



& Holm (K.), *Biochem. Ztschr. (Berl.)*, 1922, **132**, 138-153; see also Klin. Wchnschr. (Berl.), 1922, **1**, 1695-1696.

When dogs and rabbits are adrenalectomized at one operation they show symptoms of prostration, lessened reaction to external stimuli, air hunger and respiratory inhibition, following which the heart continues to beat for a time. There is also a drop in the blood sugar, but death is not dependent upon the course of this fall. Relatively high as well as relatively low values are found. The same is true of the glycogen content of the liver. Liver glycogen and blood sugar are nevertheless related. Pilocarpin causes a rise but of lesser degree than normal in adrenalectomized animals. CO-glycemia is also produced in adrenalectomized rabbits if the animals are given atropin. It is therefore dissimilar to the pilocarpin reaction. Blood gas analyses showed that pilocarpin glycemia is not accompanied by asphyxia. It cannot be influenced by O-inspiration.

—F. S. H.

(ADRENALS) Addison's disease in early infancy (*Malattia di Addison nella prima infanzia*). Cannata (S.), *Pediatria (Napoli)*, 1922, **30**, 585-590.

Case report of a 16 months' old child.—G. V.

The effect of the blood-sugar level on ADRENAL secretion and sympathetic activity—a preliminary note. Cannon (W. B.), McIver (M.) & Bliss (S. W.), *Boston M. & S. J.*, 1923, **189**, 141-142.

Experiments were carried out on cats in which the heart was isolated from the nervous system by Cannon's method. Chloralose was used as an anesthetic. The blood sugar was reduced by injections of insulin. When the percentage fell below 0.1 to 0.07% in cats with intact adrenal glands there was an increase in the heart rate and a checking of the fall in sugar percentage. If the adrenals had been removed or isolated from the nervous system these changes did not occur and the reduction of sugar in the blood continued until the animal died. These results show a mechanism for maintaining the normal percentage of blood sugar in which the sympathetic control of the discharge of adrenin plays an essential part.

—J. C. D.

The ADRENAL cortex in diphtheria. Clevers & Goormatigh, *Bull. Acad. roy. méd. Belg.*, 1922, [5] **2**, 425-438.

Cholesterol normally on microscopic examination is limited to a narrow layer in the adrenal of guinea-pigs. This zone widens after injection of diphtheria toxin, during which time some passes into the blood, and the excretion of a "lipoproteic" substance increases.—*Physiol. Abst.*, **8**, 223.

The effect of asphyxia upon the ADRENAL output as demonstrated by variations in the temperature of the brain. Crile (G. W.), Rowland (A. F.) & Wallace (S. W.), *Am. J. Physiol. (Balt.)*, 1923, 66, 304-308.

"Asphyxia produces an increased output of epinephrin which is manifested by an increase in the temperature of the brain."

—T. C. B.

Syphilis of the ADRENALS (Ein seltener Fall von Lues der Nebennieren). Crohn (W. H.), *Med. Klin. (Berl.)*, 1922, 18, 1512-1513.

The case is reported of a man with anemia (hemoglobin, 15% Sahli; erythrocytes, 1,650,000) and abnormal pigmentation, especially on the body. The blood pressure was 95/45. During antiluetic treatment the pigmentation disappeared, the anemia was ameliorated (hemoglobin, 60% Sahli) and the Wassermann reaction became negative. The patient was finally dismissed as cured. The author believes that this was a case of syphilis of the adrenals.

—W. R.

(ADRENALS) Some effects of strychnine and physostigmine upon the blood picture. Edmunds (C. W.) & Lloyd (P. C.), *Am. J. Physiol. (Balt.)*, 1923, 63, 392 (Proc.).

The administration of small doses of epinephrin produces a typical change in the relative numbers of the white blood cells. It was thought that possibly this reaction might be used as an index of increased activity of the adrenal glands and in addition perhaps furnish an explanation for some of the effects of strychnine and physostigmine, which have been shown to stimulate these glands. The administration to dogs of these two alkaloids is followed by an increase in the number of white blood cells which resembles exactly that produced by epinephrin. After removal of the adrenal glands from dogs and subsequent administration of the two alkaloids, instead of an increase in white cells, there is in every case a decrease, hence the leucocyte increasing effect of these drugs is due to their stimulating the adrenal glands. In addition to the changes in the white blood cells, physostigmine in still larger doses causes a marked increase in red cells, which increase resembles that produced by epinephrin with the exception that it is not prevented by the administration of ergotoxin.

(ADRENALS) A case of Addison's disease, rapidly fatal. Fleming (C. M.), *Brit. M. J. (Lond.)*, 1922 i, 951.

Fleming reports a rapidly fatal case of Addison's disease in a boy, aged 17, which presented the following remarkable features: (1) the practically complete absence of suprarenal tissue and the length of time this condition must have existed before death; (2)

the marked activity of the thyroid gland, probably compensatory in nature, affording evidence of the correlation of function of the two glands; (3) the persistence of the thymus in view of Wiesel's suggestion that adrenal insufficiency hinders its involution.—*Med. Sc.*, 8, 292.

(ADRENALS) Addison's syndrome in malaria. Fulchiero (A.), *Policlin.* (Roma), 1923, 30, 426-432.

Fulchiero's three patients presented apparently typical Addison's disease, but under treatment for malaria, and epinephrin, the Addison syndrome subsided, except the pigmentation. This persisted practically unmodified.—*J. Am. M. Ass.*, 81, 256.

The physiological action of ADRENAL blood (*Expérience susceptible de démontrer l'action physiologique du sang surrénal*). Gley (E.) & Quinquaud (A.), *Compt. rend. Soc. de biol.* (Paris), 1923, 88, 1121-1123.

During excitation of the splanchnic the blood from the supra-renal vein of the same side is collected. The time is noted and the blood is reinjected into the cardiac end of the renal vein of the same side, exactly the same time being taken for injection as was taken for its collection. A typical rise of pressure was obtained in 10 out of 15 dogs. Negative results were obtained in cats and rabbits. It appears that adrenal discharge under the influence of splanchnic stimulation is not always sufficient to manifest its action; the phenomenon is not constant.—*T. C. B.*

Production of epinephrin by the ADRENAL cortex. Hartman (F. A.), *Science* (N. Y.), 1923 n. s., 58, 74.

Slices of cortex taken from the adrenal of a cat gave a positive colorimetric test for epinephrin. Likewise where the medulla had been previously destroyed the cortex by various tests gave evidence of containing epinephrin.—*G. E. B.*

Conditions determining ADRENAL secretion. Hartman (F. A.), McCordock (H. A.) & Loder (M. M.), *Am. J. Physiol.* (Balt.), 1923, 64, 1-34; see also, *ibid.*, 63, 405 (Proc.).

The superior cervical ganglion was removed one week before the pupil was completely denervated by removal of the ciliary ganglion. The technique of the operation is given. All possibility of central nervous influence being thus eliminated, the denervated pupil can be influenced only by the circulation, and becomes a reliable test for epinephrin. It was found that barking dogs had no effect on the epinephrin output in the cats studied. Stimulation of the pinna, cold, asphyxia, operations, etc., all produce a dilatation of the pupil, as a result of increased secretion of epinephrin. The observations indicate an emergency function of the adrenals.

—*T. C. B.*

The production of epinephrin by the ADRENAL cortex. Hartman (F. A.) & Hartman (W. E.), *Am. J. Physiol. (Balt.)*, 1923, **65**, 623-634.

The adrenal cortex gives the Folin, Cannon and Denis test; it inhibits contracting intestine and causes dilatation of the sensitized pupil. It is concluded that the adrenal cortex appears to produce epinephrin.—T. C. B.

Pathology of the ADRENALS (*Beiträge zur pathologischen Anatomie der Nebennieren*). Huebschmann, *Beitr. z. path. Anat. u. z. allg. Path. (Jena)*, 1921, **69**, 352.

The author describes and discusses a case of atrophy of both adrenals, and a case of atrophy of one adrenal with hyperplasia of the other. The first case was similar to another one described by Marchand in 1909; the second case was particularly interesting because of luetic origin.—*Med. Sc.*, **8**, 141.

The effects of SUPRARENAL injury (by removal or freezing) on the interstitial cells of the OVARY. Jaffe (H. S.) & Marine (D.), *J. Exper. M. (Balt.)*, 1923, **38**, 93-106.

The interstitial cells of the ovary and the cells of the adrenal cortex undergo hypertrophy simultaneously in certain animals during pregnancy and removal of the gonads is known to cause hypertrophy of the adrenal cortex. The authors studied the effects of various types of adrenal injury on the interstitial cells of the gonads in nearly 400 rabbits. Partial adrenalectomy was performed in 13 rabbits and complete adrenalectomy in 30 rabbits. Moderate or marked ovarian enlargement due to hypertrophy of the interstitial cells was observed in 76% of the rabbits that survived double adrenalectomy over 30 days. Partial adrenalectomy had little or no effect. The hypertrophy of the interstitial cells is looked upon as a compensatory reaction and adds further proof to the theory of a functional interrelation between the adrenal cortex and the interstitial cells.—I. M.

The effects of SUPRARENAL injury (by removal or freezing) on the tubules and interstitial cells (Leidig) of the TESTIS. Jaffe (H. L.) & Marine (D.), *J. Exper. M. (Balt.)*, 1923, **38**, 107-115.

The testicles of 48 double adrenalectomized and of 45 partial adrenalectomized rabbits were examined. There were no specific changes either in the tubules or in the interstitial cells—a marked contrast to the hypertrophy in the ovary. The authors believe this to be an indication that the interstitial cells of the testis and ovary are not functionally homologous.—I. M.

Cholesterin metabolism after ADRENAL extirpation (*Contribución al estudio del metabolismo de la colessterino—Estudio experimen-*

tal de la colesterinemia en diez ratas, antes y despues de la extirpación de ambas capsulas suprarrenales). Julio (G.), Prensa méd. argentina (Buenos Aires), 1923, No. 35, 1014.

Three rats 3 days and three 6 days after double decapsulation had a normal amount of cholesterin in the blood.—B. A. H.

Ablation of the ADRENALS and epilepsy (Nebennierenreduktion und epileptischer Krampf). Kutscha-Liszberg (E.), Wien. klin. Wchnschr., 1923, 36, 443-447.

In 11 cases of epilepsy an adrenal was removed. Two years later the patients were observed again. One had had no more attacks; in 6 the attacks had become rare; in 4 no improvement was seen. However, 1 of these patients had had in his youth a severe disease of the central nervous system; in a second subject the operation was not perfectly performed (probably the adrenal was not completely removed); and in a third the adrenal was abnormally small.—J. K.

The value of Sergent's white line in the diagnosis of ADRENAL insufficiency (Sobre el valor de la raya blanca de Sergent en el diagnóstico de la insuficiencia suprarrenal). Marañón, Med. ibera (Madrid), 1923, No. 277, 174-177.

Acute adrenal insufficiency is characterized by asthenia, hypotension and rapid pulse, symptoms similar to those of post-infectious myocarditis, diagnosis of which is impossible. The same difficulties are encountered when fulminating adrenal insufficiency manifests itself in meningitis, encephalitis or acute peritonitis. In all these cases in which the typical pigmentation of chronic adrenal insufficiency is lacking the clinics have reported certain signs of adrenal lesions, among others, Sergent's white line. This is not a symptom of hypotension, however, but a vasomotor phenomena indicating irritability of the vegetative system not allied to any determined disorder, and is not a basis for diagnosis of obscure states of adrenal insufficiency.—E. B.

Function of the ADRENAL (Beiträge zur Physiologie der Drüsen, von Leon Asher. No. 55. Fortgesetzte Untersuchungen über die Function der Nebennieren). Marti (H.) Ztschr. f. Biol. (München), 1922, 77, 181-198.

The experiments were made on white rats: (1) after removing both adrenal glands and (2) after removing the adrenals and then castrating to remove the accessory adrenal material in the epididymus. These latter are called completely adrenalectomized animals. They survive the complete operation without apparent inconvenience. The animals were tested in a chamber giving a reduced oxygen tension, the length of time they took to collapse being considered a comparative measure of the functional power of the heart.

Normal and adrenalectomized rats behaved the same way under reduced oxygen tension. Completely adrenalectomized animals collapse more rapidly than the normals, indicating a reduction in the functional power of the heart. Administration of thyroid tablets to adrenalectomized animals caused the characteristic reduction in resistance to collapse, but not as markedly as in normal animals. Adrenalectomized animals showed a sharp temporary increase in weight in the first 3 days of thyroid feeding. Some of these conclusions are based on very few experiments.—J. C. D.

**ADRENAL discharge in the dog.** Searles (J.), *Am. J. Physiol.* (Balt.), 1923, 66, 408-413.

Asphyxia and sciatic stimulation in the dog increase the rate of the denervated heart; there is no increase in fasting dogs if the lumbo-adrenal veins are occluded.—T. C. B.

**The ADRENALS and pancreatic DIABETES.** Stewart (G. N.), & Rogoff (J. M.), *Am. J. Physiol.* (Balt.), 1923, 65, 319-330.

It has been maintained that the presence of the adrenals is necessary for the development of pancreatic diabetes. No experimental basis for such a theory is found.—T. C. B.

**The significance of the Zuckerkandl's organ and its relation to the SUPRARENAL MEDULLA of children.** Tokumitsu (M.), *Chosen-Igakukai-Zasshi* (Keijo), 1923, No. 43, 69-74.

The author carried out histological examinations of Zuckerkandl's organ and of the suprarenal medulla on children. He found that the former gradually degenerates after 2 years of age, while the latter develops. The chrom reaction was evident in the former, especially after 2 years of age, but it was never found in the latter. Therefore, the author concluded that Zuckerkandl's organ compensates for the incompleteness of the function of the suprarenal medulla during childhood.—S. K.

**ADRENAL hematoma in a newborn infant** (*Consideraciones sobre un caso de hematoma suprarrenal en el recién nacido*). Velasco Blanco (L.) and Paperini (H.), *Arch. Conf. med. d. hosp. Ramos Mejia*, 1923, 7, 14.

Death occurred 3 days after painful delivery with forceps. During the life of the infant there was marked jaundice. There was blood in the peritoneum and a large subcapsular hematoma of the liver. In the 2 adrenals were 2 voluminous hematomas.—B. A. H.

**(ADRENALS)** Note on the abdominal chromaffin body in dogs. Wislocki (G. B.) & Crowe (S. J.), *Johns Hopkins Hosp. Bull.* (Balt.), 1922, 33, 377-379.

The chromaffin body in the dog has not more than one-fourth the volume, and one-twelfth the amount of active substance found in

the adrenal medulla. The authors studied this body in 10 dogs which died as a result of removal of all the medullary tissue and most of the cortex of the adrenal glands, followed by destruction of the remaining cortical cells with radium. The chromaffin staining reaction was not greatly changed and the bodies were not enlarged. It is suggested that this body may be sufficient to supply the needs of the body after destruction of the medulla of the suprarenals.

—J. C. D.

**Effect of ADRENALIN in malnourished pigeons (Intoxication et carence. Effets de l'adrénaline sur la carence expérimentale du pigeon).** Arloing (F.) & Dufourt (A.), *Compt. rend. Soc. de biol. (Par.)*, 1923, 88, 1037-1038.

Adrenalin appears to hasten the appearance of signs of malnutrition in pigeons subjected to a diet of polished rice.—T. C. B.

**The calorogenic action of ADRENALIN chlorid.** Boothby (W. M.) & Sandiford (I.), *Am. J. Physiol. (Balt.)*, 1923, 66, 93-122.

Evidence to show that adrenalin intravenously injected in doses within the power of the adrenals to secrete, actually increases the rate of heat production, probably by increasing the heat production of nearly all types of cells. The R. Q. is elevated, and blood sugar slightly concentrated.—T. C. B.

**The calorogenic action of ADRENALIN chloride.** Boothby (W. M.) & Sandiford (I.), *Am. J. Physiol. (Balt.)*, 1923, 63, 407 (Proc.).

There is a direct chemical stimulation of cellular combustion. The rate of transformation of potential into kinetic energy is accelerated by adrenaline.—*Physiol. Abst.*, 8, 139.

**Cardio-vascular reactions response to ADRENALIN or to suprarenal compression (Influence du tonus nerveux initial sur les réactions cardio-vasculaires consécutives à l'injection d'adrénaline ou la compression surrénale).** Gautrelet (J.) & Garibaldi (A.), *Compt. rend. Soc. de biol. (Par.)*, 1923, 89, 392-396.

Injection of adrenalin in pilocarpinized animals causes a marked retardation of cardiac rhythm. Compression of the suprarenals has no effect in the normal cat, but after injection of pilocarpin or strychnin the same compression causes hypertension.—T. C. B.

**Does ADRENALIN affect the metabolism of the surviving skeletal muscles of the frog?** Griffith (F. R. Jr.), *Am. J. Physiol. (Balt.)*, 1923, 65, 15-29.

Using a modified Osterhout apparatus it was found that adrenalin had no effect on the CO<sub>2</sub> production of isolated frog's muscle, nor on the total acid production.—T. C. B.

Influence of temperature changes on the secretion of EPINEPHRIN. Hartman (F. A.) & Hartman (W. B.), *Am. J. Physiol. (Balt.)*, 1923, 65, 612-622.

Making use of the denervated pupil as an indicator, it was found that cooling the skin by ice, cold water or evaporation causes an increase in epinephrin output. The increase takes place in the absence of excitement and struggling, and may be due to stimulation of the periphery.—T. C. B.

Conditions of ADRENALIN activity and substances in the blood causing contraction of the blood vessels (*Zur Frage der Blutdrucksteigerung. I. Experimentelle Untersuchungen über die Bedingungen der Adrenalinwirkung. II. Untersuchungen über gefäßsverengernde Stoffe im Blute*). Hülse (W.), *Ztschr. f. d. ges. exper. Med. (Berl.)*, 1922, 30, 240-267, 268-292; abstr., *Ber. ü. d. ges. Physiol. (Berl.)*, 1923; 18, 108.

Perfusion of Laewen-Trendelenburg's frog preparation with isotonic NaCl solution in the presence of an alkali increases the action of adrenalin, as does KCl in smaller concentrations; in the presence of slight acidity a greater concentration of KCl is needed. CaCl<sub>2</sub> has a diminishing effect. Na is necessary for the development of adrenalin action. With an increasing osmotic pressure the sensitiveness of adrenalin decreases. If the molar NaCl concentration is reduced there is an initial rise followed by a decrease of adrenalin activity. Sodium citrate retards the destruction of adrenalin and thus promotes the action of this body in the organism. It was shown by the use of a perfusion solution for detecting adrenalin in experimental blood that adrenalin could be determined only on its way from the point of its formation to the right heart. Even in hypertonic subjects no adrenalin could be found in arterial blood.

—R. G. H.

ADRENALIN and its influence on circulation (*Adrenalin und sein Einfluss auf den Kreislauf*). Prusfk (B. K.), *Casop. lék. česk. (v Praze)*, 1922, 61, 1079-1110; abstr., *Ber. ü. d. ges. Physiol. (Berl.)*, 1923, 17, 363.

Twelve patients were subcutaneously injected with 0.6 to 1.0 cc. of adrenalin. The blood pressure was measured at 1 to 2 minute intervals; the pulse rate and electrographic records were taken each at intervals of 3 to 5 minutes. The author also noted the general and local symptoms. He found no typical reaction in 2 subjects as to rise in blood pressure and acceleration of pulse; in 4, there was little reaction; in 3, a decided, typical reaction; in 1, a very strong reaction. Three patients with irregular heart rhythm were experimented upon (1 case of "extrasystolic" arrhythmia and 2 of "auricular fibrillation"). The author concludes that adrenalin in human beings sometimes strengthens the auricular contractions and usually



increases the ventricular contractions by direct action on heart muscle or on nerve endings themselves. By this influence on the sympathetic nerve endings the pulse rate is increased; in the blood vessels of the extremities there is active vasodilatation and contractility is increased, this being sometimes the only effect of adrenalin. The cutaneous capillaries are narrowed and in this way resistance is raised. The blood pressure primarily rises from increased cardiac activity. The minimal pressure falls following the widening of the large vessels in the extremities, even during strong capillary contractions. The author obtained these results by following Lombard-Weisszschén's method.—R. G. H.

**On the effect of ADRENALINE on the nature of the blood sugar.**  
Winter (L. B.) & Smith (W.), *J. Physiol. (Lond.)*, 1923, 57, liii.

The mixture of sugars present after injection of adrenaline appears to be similar to that existing in diabetic blood before injection of insulin. Phenyl-osazones have been prepared from the blood of rabbits after adrenaline, and from the blood of diabetics; crystalline osazones other than glucosone have been observed.

—*Physiol. Abst.*, 8, 251.

**The ENDOCRINE causation of scleroderma including morphea.**  
Castle (W. F.), *Brit. J. Dermat. & Syph.*, 1923, 35, 303.

The author believes that the essential cause of scleroderma is a combination of a disordered function of the incretory glands, together with an affection of the nervous system. It is more than probable that the internal secretory system acts as a whole and if any particular gland fails, the remainder of the glands act to minimize that failure. Therefore, it is impossible to fix the responsibility upon any particular gland. Severe nervous emotion must be considered as a possible cause, owing to its influence on the sympathetic nervous system which is closely related to the endocrine glands. In some cases, no history of shock nor prolonged mental strain can be elicited, and here the endocrine failure may be due to long continued poisoning, such as focal infections. He believes that the thyroid is the principal gland which has a marked bearing upon scleroderma, as disorders in the thyroid are frequently found associated with scleroderma. The adrenal and pituitary glands do not seem to be involved. The author states that because an extract of a gland causes improvement or cure, it is wrong to assume that that particular gland is the one which is deficient.—L. K. McC.

**Case of masculine osteomalacia. Study of ENDOCRINE glands (Un cas d'ostéomalacie masculine. Etude des glandes à sécrétion interne).** Chabrol (E.) & Haguenau. *Bull. et mém. Soc. méd. d. hop. de Par.*, 1923, 47, 973-977.

Masculine osteomalacia is rare, being mentioned but 13 times out of 145 cases reported by Durhaun. The present case is remark-

able on account of the duration of its evolution (30 years or more). Radiographic study showed evidences of recalcification in several bones. Of the endocrine glands the adrenals showed the most marked deviations from normal. They were very large; the left one weighed 30 gms.—F. S. H.

The present position of **ORGANOTHERAPY**. Cobb (J. G.), Practitioner (Lond.), 1923, 111, 278-290.

An enthusiastic defense of empirical organotherapy against the recent criticism to which it has been subjected.—J. C. D.

The present status of **ENDOCRINE therapy**. Cohoe (B. A.), Atlantic M. J. (Harrisburg), 1923, 26, 602-606.

The author enumerates the various popularly employed glandular products, pointing out the facts and fallacies associated with their use. The most important statement in the paper is the following: "Polypharmacy in the form of pluriglandular mixtures has of late run riot. The promulgation of an alluring hypothesis of the selective capacity of the organism to pick out from the blood the hormones it requires and to discard the others, simultaneously with the flooding of the physician's mail with enticing literature extolling the therapeutic marvels of the endocrines on the part of some, fortunately not all, of the pharmaceutical companies, is in a large measure responsible for this deplorable state of affairs. . . . Happily for the patients, the majority of these pluriglandular mixtures are inert when administered by mouth, except for the thyroid substance they may contain. . . . Only by avoiding an indiscriminate and reckless form of pluriglandular therapy can the conscientious clinician hope to escape the odium that has in some quarters attached itself to glandular treatment and to prevent the legitimate field of endocrine therapy from falling into disrepute."—I. B.

**ENDOCRINOLOGY** in criminal anthropology (*L'endocrinologia in antropologia criminale*). DeTullio, *Riforma med.* (Napoli), 1923, 39, 113.

Endocrine dysfunction is found in a large percentage of criminals.—G. V.

**ENDOCRINE GLANDS** and anaphylaxis (*Glandes endocrines et anaphylaxie*). De Waele (H.), *Arch. internat. de physiol.* (Liège), 1923, 21, 205-214.

Thyroid, adrenal and anterior hypophysis injection tends to diminish vagus tonus and to increase sympatheticotonus. Thus it favors the appearance of peptone shock. On the contrary, parathyroid and posterior hypophysis injection increases vagus tonus; the phenomena of shock are delayed, and in the rabbit may be prevented. Thyroidectomy renders the rabbit vagotonic, and shock is not pro-

duced or is slight. After 20 to 30 days the animal is again capable of the reaction. If one gives the thyroidless animals a thyroid injection, the capacity for reaction reappears, while if one gives parathyroid, the resistance to shock is maintained. From the fact that adrenal injection restores the reaction in a thyroidless rabbit, possibly the reappearance of the reaction after 20 or 30 days may be due to the hyperfunction of the adrenals.—W. B. C.

Some ENDOCRINE aspects of the psyche. Hammar (J. A.), *Folia neuro-biol.* (Haarlem), 1922, 12, 209-230.

A general discussion. The author points out the undoubted effect produced by the thyroid, gonads, etc. This is an elective action of the hormone on certain portions of the nervous system analogous to that exerted by certain drugs. We lack knowledge of where this action takes place. The nervous system in turn has an action on the endocrine system. This system is particularly associated with the sympathetic system. There are, therefore, probably psychic effects of endocrine origin which have not yet been clearly associated with any given organ. The author says: "The chief use of a summary of this sort lies in its strong emphasis of important gaps in our present knowledge and what might be gained by filling these gaps."

—J. C. D.

(ENDOCRINE) Constitution and disposition (Konstitution und Disposition). Hart (C.), *Ergebn. d. allg. Path. u. path. Anat.* [etc.] (Wiesb.), 1922, 20, 1-435; abst., *Berl. ü. d. ges. Physiol.* (Berl.), 1923, 17, 17.

Hart's study is based on nearly 2000 articles from the literature. Although the voluminous foreign literature of late years was not taken up in detail, the principal theories of the foreign schools were considered. Constitution is defined as the sum of a person's inherited characteristics, the determined developmental and reactionary activity of the organism due to combinations of the existing inherited factors. Aside from this appear acquired characteristics, either as beneficial or harmful somatic variations. It is only through research in the field of heredity with a strictly established distinction between inherited and acquired characteristics that a clean-cut impression can be gained concerning the idea of constitution. A deviation of the constitution is any anomaly occurring beyond the normal variation limit; this may occur through excess or deficiency of normal, or through the existence of inherited pathological factors. Frequently recurring anomalies are always transient conditions from a normal to a pathological state and have led to the establishment of pathological types of constitution. A diathesis is a particular combination of many pathologically changed hereditary factors. The idea of constitutional diseases is unwarranted. The constitutional inclination of an organism or of its parts (other than disease) falls

under the heading of disposition, acquired inclination, or both. Co-ordinated peculiarities which are extensively spread out over certain tissues or organs, building up their foundation, give characteristic features. Disharmony in the endocrine system plays an important rôle in the formation of types of constitution. Some peculiarities of the constitution which are taken as signs of degeneration are only normal deviations from the ideal limits of variation. Detailed discussions are given of the so-called status thymicolymphaticus, accidents and sudden death, special relationship to the organs of internal secretion, the state of the lymph glands and the thymus in infectious diseases, Addison's disease, Graves' disease, etc. An insight is given into the difficulties of diagnosis. The author concludes that status lymphaticus is not a clear constitutional hyperplasia of the lymph system, but that it is always a secondary form of reaction following an internal or external lesion. On the other hand, he believes that status thymicolymphaticus is due to some disorder in the incretory system, under the domination of the thymus. Exudative diathesis is related to status thymicolymphaticus. It is difficult to determine whether these disturbances should be treated as inherited or acquired disorders. Infantilism, like the foregoing, is treated according to its outward manifestations and causal conditions. It is treated as a result of continued arrest of an organ or body part in a transient phase and is thought to be closely connected with the endocrine system. There is no universal type of infantilism. Disturbances of the endocrine organs can be co-ordinated with all other organs. Disorders of the incretory organs may be predominant or they alone may be affected. A pluriglandular disturbance is nearly always present. A fundamental distinction cannot be made between infantilism and eunochoidism, because this, as well as pluriglandular disturbances, must be considered as under the control of the participating embryonic glands, whether primary or secondary. Mongolism, like infantilism, is also due to endocrine disorder and is recognized both by bodily and mental manifestations. It is concluded that mongolism is not a true type of constitution, since no hereditary condition seems to exist. In *asthenia universalis* the circulatory system apparently plays no part. This condition is due to a general functional weakness, to a lack of energy in normal development and to the histological state of the tissues and organs. Since the endocrine system is also subject to functional weakness, a relationship is apparent. Differentiation of the types of constitution is difficult because they are so often closely associated. Hart concludes with a warning against the uncritical use of the idea of constitution and against overestimation of the rôle of the constitution in the bodily and mental fields.—R. G. H.

(ENDOCRINE) Syphilis of the sympathetic system (*La syphilis du grand sympathique*). Lévy-Franckel (A.) & Juster (E.), *Ann. d. mal. vén. (Par.)*, 1923, 18, 1-23.

The authors, in a review of syphilis of the sympathetic system, remark on the close association between the sympathetic system and the endocrine glands in this connection. They attempt to distinguish between conditions in which the sympathetic is affected primarily, and those in which it is affected secondarily to lesions of the endocrine glands. In the first category they place Raynaud's disease and paroxysmal hemoglobinuria; some cases of vitiligo, acanthosis nigricans, alopecia areata, cardiac arrhythmia and exophthalmic goiter. With regard to the latter, the authors remark that in syphilis all stages occur between tachycardia with or without exophthalmos and confirmed exophthalmic goiter; also that the condition is not seldom found in tabetics. The rôle of the sympathetic system is shown by diminution in the pilomotor and oculocardiac reflexes, similar to what occurs in alopecia areata, which is often associated with exophthalmic goiter. In the second category the authors include myxedema and Addison's disease, some cases of which have been proved of syphilitic origin. They point out that syphilis (or heredo-syphilis) is to be regarded as only one of several causes of these sympathetic and endocrinal disorders, and that evidence of syphilis varies considerably in the different affections. For instance, it is frequently found in alopecia areata, vitiligo, exophthalmic goiter, etc.; but cases of acanthosis nigricans and Addison's disease of proved syphilitic origin are rare.—*Med. Sc.*, 8, 488.

The ENDOCRINE glands and epilepsy (*Glandes endocrines et épilepsy*). Marchand (L.), *Rev. Neurol. (Par.)*, 1922, 29, 1435-1466.

The author believes that there is only a restricted number of observations in which one can admit that the endocrine disturbance has caused the epilepsy.—C. E. N.

Lesions of the ENDOCRINE glands in a case of dementia precox (*Lésions des glandes endocrines dans un cas de démence précoce*). Merland (A.) & Florentin (P.), *Compt. rend. Soc. de biol. (Par.)*, 1923, 89, 333-335.

In a subject with dementia precox, dying at the age of 36, profound alterations were found in the hypophysis thyroid and testicle.  
—T. C. B.

The pathology of the DUCTLESS GLANDS in a series of dementia praecox patients. Morse (M. E.), *J. Neurol. & Neuropath. (Lond.)*, 1923, 4, 26.

Pathological studies of the ductless glands in 12 male and 15 female dementia praecox patients dying under 45 years of age. Control cases were studied. The condition of the sex glands of the

controls was essentially the same as in the dementia praecox subjects for the terminal cases, with the exception of the feeble-minded, the infantile and the emaciated. A little less than half of the subjects presented fibrosis of the pituitary, which could be correlated to some extent with a similar condition in the gonads. As demonstrated by the controls, this fibrosis in the pituitary is not peculiar to dementia praecox, but depends rather on the nature and duration of the terminal disease and the state of nutrition. The influence of tuberculosis in producing a fibrous increase in the ductless glands, especially in the gonads and pituitary, has been emphasized once more by the study of this series.—C. E. N.

**INCRETORY** influence upon the human capillary system (Ueber hormonale Beeinflussbarkeit des Kapillarsystems beim Menschen). Redisch (W.), München. med. Wchnschr., 1923, No. 19, 589-592.

Observations of the nail-notch capillaries after subcutaneous injection of 0.001 of adrenalin show a spasm-like narrowing and at the same time increased blood pressure; the latter endures longer than the capillary reaction. In cases of diabetes mellitus the action of adrenalin on the capillaries continued twice as long as in non-diabetics and was more intensive. The blood pressure showed a similar reaction. Injection of ovoglandol caused dilatation of the capillaries and decreased blood pressure. Adrenalin and ovoglandol injected at the same time caused a remarkable abridgment of the typical adrenalin reaction on capillaries and blood pressure. There is probably an antagonistic reaction between adrenalin and the ovarian hormone in the capillary system.—W. R.

Diseases of **DUCTLESS GLANDS**. Rolleston (J. D.), et. al., Med. Sc. (Lond.), 1923, 8, 284-299.

A review of recent literature.—R. G. H.

**INTERNAL SECRETION** between mother and fetus. Tanberg (A.), Acta med. Scand. (Stockholm), 1922, 56, 33-51.

The incretory glands of the fetus do not act as long as those of the mother are intact. (In these experiments the thyroid was investigated.) If the gland is removed from the mother, that of the fetus proceeds to act. The secretion, however, does not reach the mother organism, the placenta being apparently impermeable to it in this direction.—Physiol. Abst., 8, 68.

**Anaphylaxis and INTERNAL SECRETIONS** (Anafilassi e secrezioni interne). Piazza (C.), Riforma med. (Napoli), 1922, 38, 1105-1106.

Animals after posterior lobe hypophyseal extract are even less resistant than the controls to anaphylactic shock; the same result was obtained in the few animals which survived intensive thyroid

treatment long enough to reach the period of anaphylactic injection. Experimental hyperthyroidism in rabbits does not modify the insensibility towards peptone and renders the anaphylactic shock more severe.—G. V.

**INTERNAL SECRETIONS and pregnancy** (Innere Sekretion und Schwangerschaft). Tomor (E.), Arch. f. Frauenk. u. Eugen. (Leipz.), 1921, 7, 111-121.

Until a certain stage of development the endocrine glands in the embryo have open secretion channels. The incretions flow through the embryo's own lymph system (for instance, from the pituitary and thyroid into the intestine) as long as these channels are open, and not directly into the mother's blood. This happens only if the channels are closed. The different physiological and pathological reactions during pregnancy are probably due partially, therefore, to the embryonic hormones which pass the placenta and whose variety explains the various pregnancy reactions better than a hypothetic placenta hormone alone. This theory is confirmed by the possibility of provoking pregnancy reactions with fetal extracts. The author believes that carbohydrate tolerance in pregnancy is affected by the thyroid, pituitary and adrenals of the embryo.

—A. B.

**The INTERNAL SECRETIONS in their relationship to mental disturbance.** Tucker (B. R.), Am. J. Psychiat. (Balt.), 1923, 2, 259-272.

In 37 subjects of well recognized mental types in whom an endocrine study was attempted it was found that 22 were pituitary dominant, 3 were thyroid dominant, 3 were suprarenal dominant, 5 were ovarian dominant and in 4 the pluriglandular disturbance was so evenly distributed that no particular gland could be said to be dominant. In all except one case more than one gland appeared to be affected. The dominant gland affected did not seem to regulate the type of mental disturbance found.—C. E. N.

**(ENDOCRINE) Iodine treatment of arteriosclerosis** (Die Beziehungen der Jodtherapie der Arteriosklerose zu Klinik und Pathologie dieser Erkrankung). Wiesel (J.), Wien. klin. Wchnschr., 1923, 36, 252-256.

The author reports the newer results of clinical and pathological-anatomical research upon arteriosclerosis, especially concerning the injuries of vessels by infectious diseases and the extensive alteration of the thyroid which is often noted. Hyaline degeneration of vessels, especially, seems to be due to incretory influence; it is a disease of the arterioles and is ordinarily accompanied by high blood pressure. The clinical symptoms of beginning old age, which are usually regarded as arteriosclerotic, are in both sexes largely due to

senile involution of the sexual glands and to alterations in the thyroid. The author has found that the thyroid vessels are greatly altered in arteriosclerosis. Two types of so-called arteriosclerosis can be distinguished: one resembling hypothyroidism (adiposity, apathy, obstipation) and one resembling hyperthyroidism (thinness, angiospastic conditions, headaches, diarrhea). Both types are less consequences of a general arteriosclerosis than of the alterations within the thyroid. Even adrenal alterations may be perceptible (hypotonia, abnormal pigmentation). Iodine treatment should be employed in accordance with the individual reaction of the patient. It is sometimes advocated in cerebral disorders and in hypothyroidism (although cautious organotherapy is usually better). The author warns that iodine treatment can do more harm than good.

—W. R.

**Hypertensive action of the carotid blood during excitation of the splanchnic** (*Action hypertensive du sang carotidien recueilli pendant l'excitation du splanchnique*). Zunz (E.) & Govaerts (P.), *Compt. rend. Soc. belge de biol.*, 1923, 1, 652-653; *abst. Physiol. Abst. (Lond.)*, 1923, 8, 183.

During the excitation of the splanchnic of dog A the arterial blood sometimes produces hypertension in dog B. This action is in evidence when a rapid crossed transfusion is carried out (400 cc. of blood in 1¼ to 2 minutes). Under these conditions the carotid pressure of dog B increases 10 to 40 mm. of mercury.—R. G. H.

**The effects of GASTRIN and histamine on the movements of the stomach and intestine during hunger.** Ivy (A. C.) & Vloedman (D. A.), *Am. J. Physiol. (Balt.)*, 1923, 66, 140-144.

Gastrin and histamine in "physiological doses" have no effect on the movements of the stomach and intestine during hunger. Hunger contractions and intestinal movements are not affected by the augmented flow of gastric and pancreatic juice following the injection of gastrin or histamine.—T. C. B.

**Stimulation of the INTERSTITIAL GLANDS by ligation of the vas deferens** (*Estímulo funcional de la glándula intersticial por sección de los canales deferentes en el hombre*). Centurion (V.), *Semana méd. (Buenos Aires)*, 1921, 28, 368.

A man of 65, senile and sexually impotent, was operated upon for hernia and, unknown to him, his vas deferens was ligated. There was a general change and a return of active sexual life.

—B. A. H.

**Action of carbohydrates and MAMMARY gland extract on milk secretion** (*Azione degli idrati di carbonio e delle iniezioni di glandola mammaria sulla secrezione lattica*). Flamini, *Pediatrics (Napoli)*, 1922, 30, 919.



Hypodermic injection of mammary gland extract causes increased milk secretion, but the effect ceases when the extract is discontinued.—G. V.

(GONADS) Relation between placenta and the secretion of milk. Frankl (O.), Tr. Am. Gynec. Soc., 1923, May 21-23.

That the fetus is not the deciding factor in the secretion of milk is proved by active lactation subsequent to the expulsion of a hydatidiform mole or a dead fetus. Ovarian function in relation to lactation is distinguished by the fact, on the one hand, that castration performed during pregnancy does not preclude lactation, while, on the other hand, in the experience of animal breeders, castration is successfully resorted to for the purpose of prolonging lactation in the mother animal. Halban first asserted that it is directly the loss of the placenta that changes the secretion of colostrum into one of milk. To prove or disprove this theory the author transplanted the placenta of a mouse under the skin on the back of another mouse. In successful cases, the implanted placenta established satisfactory connection with the adjoining tissues, and the organ could be observed to persist for 3 or 4 weeks. After this time, histologic study showed a complete absorption of the grafted placenta. In these experiments the placentas of pregnant mice were employed within 10 or 12 days of full term, and transplanted under the skin of the back of mice approximately in the same stage of pregnancy. In this group of successful transplants, mice from a strain known to be able to nurse satisfactorily their young, would have litters of 5 or 6. The new-born offspring would seem normal in their appearance and would immediately begin to nurse the mother animal; but they invariably died within the next 5 to 7 days, evidently from starvation. Investigations showed that the mamma of the mother animal was secreting colostrum and not milk. The successful transplantation of a placenta on a pregnant animal causes persistence of colostrum secretion. Clinical experience points to the fact that the placenta must be regarded as an organ endowed with endocrine activity, whose function it is during pregnancy to prepare the breast glands for the secretion of milk, and simultaneously to prevent secretory activity.—J. Am. M. Ass., 81, 66.

(GONAD) Sex development and behavior in male patients with dementia praecox. Gibbs (C. E.), Arch. Neurol. & Psychiat. (Chicago), 1923, 9, 73-87.

The testicles of dementia praecox patients first admitted to the hospital between the ages of 16 and 20 years compare favorably in size with those of patients first admitted between the ages of 21 and 40. Pubic hair of a definitely feminine distribution was present in 13% of the patients first admitted between the ages of 16 and 20, and was still present in 13.4% after they were 21 years of age or

over, but was present in only 2.6% of those first admitted between the ages of 21 and 40. Deficient development of the secondary sexual hair did not depend on the size of the testicles, being associated with rather large testicles as frequently as with small ones.

—C. E. N.

**CORPUS LUTEUM of birds** (*Das Corpus luteum der Vögel*. Hett (J.), *Anat. Anz.* (Jena), 1922, 55, 153-159.

Employing principally the ovary of the domestic fowl, the author found that the corpus luteum is developed much as it is in mammals. The follicular epithelium remains for a time after the discharge of the ovum; wandering- and pigment-cells arise from the theca, and the connective tissue and blood vessels multiply. The author is unable to assign an endocrine function to the structure.

—W. J. A.

**(GONADS)** Influence of the female generative organs on basal metabolism (*Ueber den Einfluss des weiblichen Genitales auf den Grundumsatz*). Kraul (L.) & Halter (G.), *Wien. klin. Wchnschr.*, 1923, 36, 538-539.

In 5 women basal metabolism was estimated before and after castration. In every case there was a decrease of 17-30%. Myomata of the uterus may influence metabolism. In subjects without hemorrhage or anemia the basal metabolism was increased in 10 out of 11 cases. The same degree of increased metabolism was found in 5 cases of hemorrhagic metropathy caused by myomata. In cases of hemorrhage due to erosion or hyperplasia of the mucous membrane of the uterus the basal metabolism was normal. In 6 patients with increased metabolism the uterus was removed and metabolism at once became normal. In 20 cases of hyofunction of the ovary metabolism showed no typical change. Before menstruation metabolism is 10% higher, more or less, than after menstruation. Metabolism is increased by x-rays and by administration of thyroid. Injections of caseoserum have no influence.—J. K.

**(GONADS)** The compensatory reaction of the sex glands (*Über die kompensatorischen Reactionen der Geschlechtsdrüsen*). Lipschütz (A.), *Skandin. Arch. f. Physiol.* (Berl. & Leip.), 1923, 43, 45-54.

After removal of one testicle in rabbits the remaining testicle grows faster and reaches a larger size than normal. This is not a compensatory reaction. When, after partial castration, the testicular or ovarian fragments hypertrophy it is not due to interstitial cells, but general factors come into play that influence the growth of the remaining tissue.—G. E. B.

**Quantitative research on experimental HERMAPHRODITISM** (*Récherches quantitatives sur l'hermaphroditisme expérimental*). Lip-

schütz (A.) & Krause (W.), *Compt. rend. Soc. de biol. (Par.)*, 1923, 89, 220-223.

The transplantation of a quantity of ovary (guinea-pig) representing one-fourth of the testicular mass has caused a development of the mammary gland in the male similar to that of a lactating female.—T. C. B.

**Radiation of GONADS and progeny** (Keimdrüsenbestrahlung und Nachkommenschaft). Nürnberger (L.), *Monatschr. f. Geburtsh u. Gynäk. (Berl.)*, 1923, 68, 7-18.

Radiation of the gonads has no harmful effect on the progeny in man.—F. S. H.

**The occurrence and significance of the INTERSTITIAL CELLS** (Über Vorkommen und Bedeutung der Zwischenzellen). Sternberg (C.), *Beitr. z. path. Anat. u. z. allg. Path. (Jena)*, 1921, 69, 262-280.

The question of the occurrence and significance of the interstitial cells still awaits a definite solution. The only points which have been so far ascertained regard the internal secretory function of these cells and their influence on secondary sexual characteristics. But only further investigations will show how far they act as trophic organs during spermatogenesis and regeneration of seminiferous tubules, and what influence they have on the compensatory proliferations through which degenerated testicular parenchyma is replaced.

—Med. Sc., 8, 143.

**(GONADS) Hermaphroditism and the sex problem** (Der Hermaphroditismus der Frösche und seine Bedeutung für das Geschlechtsproblem und die Lehre von der inneren Sekretion der Keimdrüsen). Witschi (E.), *Arch. f. Entwcklungsmechn. d. Organ. (Berl.)*, 1921, 49, 316-358.

In here confirming and elaborating some of his previous investigations the author holds that frog hermaphrodites are always transformation forms and that the development proceeds without exception from female to male. The interstitial tissue which appears at the time of transformation assumes important functions in that it takes part, on the one hand, in the dissolution of the ova, and on the other hand, in the nutrition of the spermatogonia. According to Witschi's observations ova are never derived from spermatogonia. The germinal epithelium is the exclusive source of oöcytes. The transformation from female to male is due either to a "male" inheritance or the influence of external factors such as heat, cold, over-ripeness, etc. Asymmetrical hermaphroditism is taken to demonstrate that somatic (secondary) sex characters can be dependent on the germ gland without the intermediation of a hormone. Witschi

contends that the general belief in the dependence of these characters upon the gonads through internal secretions is not well founded.

—W. J. A.

**HYPOPHYSIS** and obesity (*Studio sopra un caso di obesità*). Barinetti, *Riforma med.* (Napoli), 1923, 39, 231.

Report of a case of obesity in a woman who died of pneumonia at the age of 37. The obesity had set in 7 years before. At autopsy the anterior lobe of the hypophysis was found to be larger than normal; the pars intermedia was greatly reduced and showed some cystic formation; the eosinophils in the anterior lobe were large and promiscuously scattered and the connective tissues showed extensive development.—G. V.

The relation of **PITUITARY** extract (infundibular lobe) to the fall of blood sugar produced by insulin. Burn (J. H.), *J. Physiol.* (Lond.), 1923, 57, xxxviii.

Instead of intensifying the fall produced by insulin, a simultaneous injection of pituitary extract either reduces, abolishes, or replaces by a rise of blood sugar, the fall due to insulin.—T. C. B.

**Epileptoid or fainting attacks in HYPOPITUITARISM.** Clark (L. P.), *Am. J. M. Sc.* (Phila.), 1922, 163, 211-218.

Clark, who records 3 cases, points out that there are a number of rapidly growing adolescents who have relatively benign fainting attacks, which at first simulate larval attacks of petit mal, but are differentiated from it by the absence of the epileptic character and the general physical and mental stigmata of epilepsy. The condition is really a part of the clinical picture of dyspituitarism, in which there appears to be an excessive functioning of the anterior lobes of the pituitary gland. The fainting attacks may be associated with low blood pressure, slow pulse, vasomotor ataxia, and numerous defective muscular and skeletal displacements. Psychically there may be character delinquencies and slow mental development. Treatment consists in physical training and administration of specific glandular substance.—*Med. Sc.*, 8, 294.

The **PITUITARY** headache in rhinological practice. Glassburg (J. A.), *N. York M. J.* [etc.], 1922, 115, 362-365.

According to Glassburg, who records 2 cases, pituitary headache, due to disturbance of secretion of the pituitary, is often met with in rhinological practice. It may coincide with morbid nasal conditions, but is entirely independent of them. It is not relieved by nasal operations, but responds to specific endocrine medication, the dosage of which varies with the subject.—*Med. Sc.*, 8, 294.

The internal secretion of the **PITUITARY** body and of the **PARA-**

**THYROID glands.** Izumi (G.), *Jap. Med. World* (Tokyo), 1922, 2, 199-200.

After extirpation of the parathyroid from rats and cats there is diminution of the chromophil cells of the anterior lobe of the hypophysis and increase of the chromophobe transition and stem cells, diminution of the hypophysis in rats, and an increase in cats due to proliferation of the cells of the pars intermedia. Thyroidectomy in cats causes hypertrophy of the anterior lobe, and very markedly of the lobus penuncularis, the pars intermedia not being affected. In the rat castration caused enlargement of the anterior lobe by the appearance and growth of "castration" cells, derived from eosinophils. Feeding of parathyroidectomized rats with phosphor-cod liver oil and calcium lactate has no therapeutic influence on teeth degeneration. Extirpation of the thyroid or castration has no effect on the development of tetania parathyreopriva.—*Physiol. Abst.*, 8, 185.

The basal metabolism in **HYPOPHYSEAL** syndromes (*Le métabolisme basal dans les syndromes hypophysaires*). Labbé (M.), Stévenin (H.), & Van Bogaert (L.), *Compt. rend. Soc. de biol. (Par.)*, 1923, 88, 1283-1285.

Two subjects with acromegaly showed an increased basal metabolism. In a case of hypophyseal infantilism and in 2 cases of adiposogenitalis the basal metabolism was diminished.—T. C. B.

Studies in **DIABETES INSIPIDUS**, water balance, and water intoxication. Larson (E. E.), Wier (J. F.), & Rowntree (L. G.), *Tr. Ass. Am. Physicians* (Phila.), 1921, 36, 409-439.

Of the 15 cases of diabetes insipidus studied 1 patient had a supratentorial brain tumor; another had a hypophyseal tumor; 4 had syphilis, and in the remaining 9 no causative factor could be determined. In 3 cases it was definitely determined that there was a sudden onset of thirst, and in 2 of these the thirst was primary, preceding polyuria. Thirst and dry mouth were complained of by the entire series of patients. Cocainization of the mouth and nasopharynx to the point of anesthesia failed to control either the polydipsia or the polyuria. Additional experiments with pilocarpin proved that the thirst is more than the mere expression of dryness of the oral mucous membrane. Studies of renal function failed to incriminate any part of the urinary tract as etiologically responsible; there were no deviations in its function except in relation to water excretion and perhaps to salt excretion. In all of the 15 subjects the urinary output was increased from 3 to 14 liters daily with a specific gravity ranging from 1.001 to 1.004. The urine chemically was practically normal. Pituitary treatment resulted in control of polyuria within 8 minutes in one subject and within 10 minutes in another. Pituitary extract yielded marked temporary results in all

patients, clinical relief lasting from a few hours to 4 or 5 days. The administration of histamin and such measures as spinal puncture, the treatment for syphilis, and the restriction of the fluid intake of the patient were practically ineffective. Metabolism studies and observations of blood chemistry before and after the administration of pituitary extract were made in 2 cases and the results tabulated. Water retention is the most prominent feature following the administration of pituitary extract, with the probability of secondary effects on the nitrogen and chlorin. In 5 normal men subcutaneous injection of 1. cc. of pituitary extract produced no appreciable effects on the urinary excretion. In dogs the subcutaneous administration of pituitary extract definitely checked the production of water diuresis, although when water was administered urinary excretion was on a somewhat higher level than normal. It was also determined that the influence of pituitary extract in the prevention of diuresis is independent of the nerve supply of the kidneys. It is impossible at present to explain the antidiuretic effects of pituitary extract. The administration to patients of quantities of water by mouth subsequent to the subcutaneous administration of pituitary extract resulted in nausea, vomiting, headache and in one instance, ataxia. Similar experiments on dogs resulted in marked tremor, salivation and occasional vomiting, while after forcing the water there developed convulsions and coma which ended fatally in one animal. The results of administration of large quantities of water without previous administration of pituitary extract were uncertain and variable. Frequently repeated doses of pituitary extract in dogs led to such toxic symptoms as diarrhea, bradycardia, arrhythmia, weakness and vomiting. The administration of quantities of water at this time gave rise to such additional symptoms as tremor, salivation, and later drowsiness, muscular twitchings, ataxia, epileptiform convulsions and coma, from which the animal recovered within a few hours. Repetition of the experiments at this point yielded recurrence of convulsions and death. Animals in which double renal nerve section had been performed reacted similarly to this experiment. The authors conclude that neither pituitary extract nor water alone is capable of producing convulsions and coma; these toxic symptoms are evidently produced by water when the water-secreting function of the kidneys is diminished through the administration of pituitary extract.—I. B.

Frölich's disease successfully treated by HYPOPHYSIS (Due casi di distrofia adiposo-genitale del Frölich trattati con l'endopofisina). Lesi (A.), Riv. osp. (Roma), 1921, 11, 361-367.

(HYPOPHYSIS) Hydrocephalus with dystrophia adiposogenitalis. Schultz, Deutsche med. Wchnschr. (Berl.), 1923, 49, 1072.

A man of 18 years, 1.45 meters in height, with a female habitus, is described. There were slight adiposity, hypoplasia of the genera-

tive organs and no secondary sexual characteristics. During life a diagnosis of tumor of the hypophysis was made. At postmortem examination hydrocephalus was seen. The midbrain was carefully examined histologically, but no changes were found.—J. K.

**DIABETES INSIPIDUS** and epidemic encephalitis. Signorelli (E.), Arch. patol. e. clin. med. (Bologna), 1923, 2, 89.

Signorelli reports a case of diabetes insipidus which occurred in a boy, aged 16, after epidemic encephalitis. Pituitary extracts were without much effect. Morphin and especially lumbar puncture (Herrick) diminished the polyuria.—J. Am. Ass., 81, 168.

The effect of **PITUITARY** feeding on egg production in the domestic fowl. Simpson (S.), Quart. J. Exper. Physiol. (Lond.), 1923, 13, 181-189.

The experiments of Clark were repeated and it was found that pituitary feeding has no effect on egg production.—T. C. B.

(**HYPOPHYSIS**) Sella turcica of mongolian imbeciles. Stevenson (G. S.) & Stultz (A. D.), Arch. Neurol. & Psychiat. (Chicago), 1923, 10, 299-303.

A radiographic study with special reference to the excavation under the anterior clinoid processes described by Timme. The authors conclude that the so-called "excavation" is present in childhood and usually disappears with development toward maturity. Its greater pronouncedness in mongolians is probably a corollary of the peculiar facial architecture and the generalized delay of bone development reported by Clift.—C. E. N.

**PITUITARY** treatment of herpes zoster. Vendel (S. N.), Ugesk. f. Laeger (Copenhagen), 1923, 85, 222-223.

The author observed 18 patients with herpes zoster, 9 of whom were treated in the usual way, locally and symptomatically, the other 9 with subcutaneous injections of 1 cc. pituitrin. Those treated with pituitrin showed a marked improvement in comparison with the other subjects. In a few hours the pain had disappeared, and in a few days the cutaneous eruption was gone. The patient should lie down for 20 minutes after the injection.—K. H. K.

The use of insulin in **DIABETIC** treatment. Allen (F. M.) & Sherrill (J. W.), J. Metab. Research (Morristown), 1922, 2, 803-985.

An extensive and comprehensive report of 102 subjects treated with insulin. The aim in treatment was to prevent over-strain of the pancreas and so allow functional improvement by maintaining the patient free from glycosuria and hyperglycemia. The tolerance of many patients was thus increased. The diet was arranged ac-

cording to the empirical needs of each patient. Slight under-nutrition with relatively smaller doses of insulin was found to be preferable to over-nutrition with large doses. The authors warn against disregarding careful dietary regulation because of the greater danger of complications. Better results have been obtained by the use of divided as opposed to single dosage in the daily routine treatment. No injurious effects were observed following the use of relatively high protein diets, approaching as nearly as possible normal relationships between the proportions of fat, protein and carbohydrate. Exercise caused an increased utilization of carbohydrates, making it a possible cause of hypoglycemic reactions in a subject with an otherwise proper adjustment between diet and the insulin dosage. Intercurrent local or generalized infections were affected by insulin therapy only in so far as it tended to improve the diabetes itself. Much larger doses of insulin were necessary in the presence of infection. Although the insulin requirement was fairly constant, the dosage had to be increased in several patients in whom glycosuria continued because of apparent pancreatic over-strain.—I. M.

**Severe DIABETES with infantilism treated with insulin** (*Diabète grave avec infantilisme traité et très amélioré par l'insuline*). Apert & Chabanier, Bull. et mém. Soc. méd. d. hop. de Par., 1923, 47, 1033-1036.

The patient excreted 8 to 12 liters of urine a day containing up to 700 gms. of sugar. He was 17 years of age, with the physical development of a boy 13. He responded well to insulin treatment.

—F. S. H.

**(PANCREAS) Conditions of glycemic regulation in the embryo** (*Conditions de la régulation glycémique chez l'embryon*). Aron (M.), Compt. rend. Soc. de biol. (Par.), 1923, 89, 189-191.

Before development of the islets of Langerhans the maternal pancreatic hormone regulates the glycemia of the fetus, but after their development the fetus regulates its own glycemia as in adults.

—T. C. B.

**New notion of the endocrine function of the PANCREAS** (*Nouvelle notion sur la fonction endocrine du pancréas*). Aron (M.), Compt. rend. Soc. de biol. (Par.), 1923, 89, 573-574.

It has been shown that the glycogenic function of the liver is coincident with the transformation of the islands of Langerhans from the embryonic to the adult type. Also the blood sugar level of the fetus differs from that of the mother. Removal of the pancreas of a pregnant bitch induces hyperglycemia in both mother and fetus. Injection of insulin into a pregnant female results in a fall of blood sugar in the fetus. It is concluded that the pancreas may have a dual endocrine function—glycogenic and glycemic.—T. C. B.



**Quantitative parallelism of INSULIN in man, dog and rabbit.** Banting (F. H.), Dobbin (G. M.) & Gilchrist (J. A.), *J. Pharmacol. & Exper. Therap.* (Balt.), 1923, 21, 191; see also Banting (H. G.), Best (C. H.), Dobbin (G. M.) & Gilchrist (J. A.), *Am. J. Physiol.* (Balt.), 1923, 63, 391 (Proc.).

The response of the diabetic dog to the subcutaneous injection of insulin shows considerable variation. Man shows a great variability in the response, but the same individual gives a relatively constant response. Rabbits (unfed for 24 hours) show considerable difference in response to insulin given intravenously. "The area included between the horizontal line drawn through the level of the normal blood sugar in the starved rabbit, and the dip of the curve obtainable by plotting the percentage of sugar in the blood over a period of 5 or 6 hours gives promise of being a useful index of probable carbohydrate utilization in man."—G. E. B.

**Acromegalic DIABETES and INSULIN** (*Diabète acromégalique et insuline*). Blum (L.) & Schwab (H.), *Compt. rend. Soc. de biol.* (Par.), 1923, 89, 195-196.

Acromegalic diabetes reacts to insulin in the same manner as pancreatic diabetes. It was thought that some insight into the nature of acromegalic diabetes might be had from its reaction to insulin, but it was not realized.—T. C. B.

**Histological study of muscle degeneration produced by local injections of INSULIN.** Bowie (D. J.) & Robinson (W. L.), *J. Lab. & Clin. M.* (St. Louis), 1923, 8, 569-572.

The authors, experimenting on rabbits, report the rather constant occurrence of marked local subcutaneous edema, somewhat mucilagenous in character, and extending for a considerable distance beyond the site of insulin injections. Histological studies of the edematous tissues revealed an absence of changes in the connective tissue cells and of abnormal degenerative deposits between the cells. However, some of the superficial muscle fibers infiltrated by insulin showed degenerative changes. Intramuscular injections caused near the site of injection a very marked degeneration of the muscular fibers and leucocytic invasion.—I. B.

**The modification of the action of INSULIN by pituitary extract and other substances.** Burn (J. H.), *J. Physiol.* (Lond.), 1923, 57, 318-329.

Simultaneous injection of pituitary extract and insulin diminishes or abolishes the fall of blood sugar produced by insulin alone. It is not the effect of an algebraic sum of the action of the 2 substances. Extracts of brain, thymus, spleen do not cause it. Pituitary extract removes the convulsions caused by insulin. The effect of small doses of insulin is increased by ergotoxin.—T. C. B.

**Ketosis, acidosis and coma treated by INSULIN.** Campbell (W. R.), J. Metab. Research (Morristown), 1922, 2, 605-635.

The author reports 14 cases varying in severity from simple ketosis to advanced coma. In all the effect of insulin was remarkably satisfactory, acting as a specific for this condition. In practically all cases glucose was administered with the insulin. The purpose of the glucose in such cases is three-fold: (1) to insure against hypoglycemia when large doses of insulin are being given; (2) to furnish energy and reduce to a minimum the incomplete combustion of fat and protein which would otherwise result in ketone production; (3) to aid in the combustion of the ketones already in the blood and tissues. One to 1.5 gm. glucose was administered for each unit of insulin until recovery was assured and diet begun. In all cases reported the ketone bodies disappeared and the carbon dioxide combining power of the blood improved. The only patients to die were those with serious infections from which death would have occurred even had diabetes not been present. Following insulin treatment the acidosis and coma showed marked remission. No alkali was used in the majority of cases, although fluids were given in abundance. Conservative use of alkali therapy in conjunction with the other forms of treatment would probably have been beneficial, in some cases at least. Patients in coma or with acidosis tolerate unusually large doses of insulin without hypoglycemia. The author could not account for a certain proportion of the insulin used in some cases, but it is suggested that this might have been used in the action on ketone bodies.—I. M.

**Insulin in the treatment of DIABETES MELLITUS.** Banting (F. G.), Campbell (W. R.) & Fletcher (A. A.), J. Metab. Research (Morristown), 1922, 2, 547-604.

Patients whose condition is too serious for successful dietetic treatment alone are the ones for whom insulin therapy is especially indicated. Insulin, in conjunction with proper dietetic treatment, is indicated in all complications of diabetes and in diabetes of any grade of severity when surgical operation is necessary. It not only affects the carbohydrate metabolism as such but causes the disappearance of ketone bodies from the blood and urine with a coincident rise in the carbon dioxide combining power of the blood. The ideal dosage is that which will cause the blood sugar to be maintained at or near the normal level while the patient is receiving a maintenance or maintenance-plus diet. This not only prevents downward progress in the disease but allows pancreatic rest.—I. M.

**Treatment of DIABETES and acidotic states with an alcoholic extract of the pancreas (insulin)** [Du traitement du diabète et des états acidotiques par l'extrait alcoolique de pancréas (insulin)].

Chabanier (H.), Lobo-Onell (C.) & Lebert, Bull. et mém. Soc. méd. d. hop. de Par., 1923, 47, 949-962.

The extract used in the 31 cases reported in this paper was prepared by the authors, who specifically state that they have had no clinical experience with the extract prepared by Macleod and his collaborators. The method, which is not given, gives a product of constant strength and amount which is very active and can be injected after neutralization either subcutaneously or intravenously without pain, and which fails to cause development of toleration. The product is titrated in units. A unit of insulin is that amount of extract which when injected into a 2.5 kilo rabbit fasted for 16 hours causes a fall in blood sugar of from 50 to 70%. The extract as prepared contains about 1 unit per cubic centimeter and is from 7 to 8 times as strong as that made in America. Clinical and physiological data lead to the conclusion that insulin is an emergency drug. Favorable effects were obtained in coma, acidosis, etc.

—F. S. H.

**Titration and toxicocity of INSULIN.** Chabanier, Lobo-Onell & Lebert, Bull. Acad. de méd. (Par.), 1923, 89, 539.

The authors found, contrary to Delezenne, that untoward effects after injections of insulin are due to the hypoglycemia which it induces, and not to the insulin directly.—J Am. M. Ass., 81, 509.

**(PANCREAS) Glucokinin. II.** Collip (J. B.), J. Biol. Chem. (Balt.), 1923, 57, 65-78.

Further observations on the effect of plant extracts on blood sugar are recorded. Various methods of obtaining potent plant extracts are given. The characteristic sign of the activity of glucokinin (low blood sugar) may be manifested from 1 day to several weeks after the injection has been made. A totally depancreatized dog was kept alive for 66 days. The animal received in all 3 injections of glucokinin (onion extract). Lawn grass has been found to give satisfactory results as a source of the compound. It was further found that animal passage of a hypoglycemia-producing principle was possible.—F. S. H.

**Action of alcoholic extract of PANCREAS (insulin) on critical glycemia** [De l'action de l'extrait alcoolique de pancréas (insuline) sur la glycémie critique]. Chabanier (H.), Lobo-Onell (C.) & Lebert (M.), Bull. Soc. chim. biol. (Par.), 1923, 5, 382-397.

Several experiments have been made with an insulin preparation made by a modification of Mackenzie Wallis' method and stated to be very active. One, with a human diabetic, is quoted in full. Injection of insulin caused an immediate disappearance of ketonuria, which did not reappear until the blood sugar had fallen to 0.105% (a fall of 55% from the original figure). The blood sugar regained

its original figure 20 hours after the insulin injection. (Cf. *Endocrin.*, 7, 113.)—A. T. C.

On glycolysis in **DIABETIC** and non-diabetic blood. Denis (W.) & Giles (U.), *J. Biol. Chem. (Balt.)*, 1923, 56, 739-744.

Glycolysis in normal blood is much more active than in the blood of persons suffering from fairly severe diabetes. This is explained by the assumption that in normal subjects the "blood sugar" consists of gamma-glucose which is readily attacked by the glycolytic enzyme, while in persons suffering from severe diabetes probably only a small portion of the reducing bodies consist of gamma-glucose, the main portion being the alpha-beta form which the glycolytic enzyme is powerless to attack. The amount of glycolysis obtained bears no relation to the concentration of the blood sugar.  
—F. S. H.

The purification of **INSULIN** and some of its properties. Dudley (H. W.), *Biochem. J. (Cambridge)*, 1923, 17, 376-390.

A method of purifying crude insulin is described. It consists essentially in precipitating the active material with picric acid and converting the insoluble picrate into a soluble hydrochloride by means of alcoholic solution of hydrochloric acid. This hydrochloride is an almost white powder of which 0.5-1.0 mg. will lower the blood sugar of a 2 kilo rabbit, which has been starved for 24 hours, to about .004% and cause typical hypoglycemic convulsions. The compound gives the biuret, Pauly and organic sulfur tests. The glyoxylic acid reaction is negative and the Millon test is faint and atypical. It contains no phosphorus. From its solutions 2 precipitates may be obtained; one by the addition of acid and the other by the addition of alkali. The first is about twice and the second about one and a half times as active as the original hydrochloride.

Both pepsin and trypsin destroy insulin. Insulin is relatively stable towards acid but is easily decomposed by alkali. It is readily absorbed in faintly acid solution, but may be filtered through Berkefeld filters without appreciable loss, if the solution is first made weakly alkaline. It appears to be a very complex protein derivative.—F. S. H.

The effect of **INSULIN** on the glycogen in the tissues of normal animals. Dudley (H. W.) & Marrian (G. F.), *Biochem. J. (Cambridge)*, 1923, 17, 435-438.

Mice were used in these experiments. The sugar which disappears from the blood of normal animals under the influence of insulin is neither converted into nor stored as glycogen either in the liver or in the skeletal muscles. The glycogen disappears from both liver and skeletal muscle after convulsive doses of insulin. There is no evidence of a conversion of carbohydrate into fat in normal animals under the influence of insulin.—F. S. H.

The effect of INSULIN on the respiratory exchange. Dudley (H. W.), Laidlaw (P. P.), Trevan (J. W.) & Boock (E. M.), *J. Physiol.* (Lond.), 1923, 57, xlvii-xlix. (Proc.)

Oxygen consumption and CO<sub>2</sub> output are decreased after injection of insulin showing that the effects produced by insulin are not due to increased combustion.—T. C. B.

INSULIN and glycolysis. Eadie (G. S.), Macleod (J. J. R.) & Noble (E. C.), *Am. J. Physiol.* (Balt.), 1923, 65, 462-476.

The uniform rate at which sugar disappears from the blood after insulin administration suggests that the increased glycolysis might be in the blood itself. If insulin could be shown to alter the rate of glycolysis in the blood *in vitro* it might be a method of assaying, and also throw light on its mechanism. The problem is stated in 4 queries: (a) Does insulin affect the rate of glycolysis in the defibrinated blood of the dog or rabbit, incubated outside the body under sterile conditions? (b) Is the rate of glycolysis the same in the defibrinated blood of a normal animal as in that of the same animal some time after injection with insulin? (c) Does insulin influence the rate of glycolysis in mixtures of muscle juice and blood or saline? (d) Does insulin influence the rate of disappearance of sugar from sterile pus? All four questions are answered in the negative. The conclusion is that the hypoglycemia is an extravascular or intracellular process; a vacuum for sugar is created, and sugar is drawn from the blood more rapidly than it can be renewed by the glycogen reserves.—T. C. B.

The effect of insulin on the metabolism of DIABETES. Fitz (R.), Murphy (W. P.) & Grant (S. B.), *J. Metab. Research* (Morristown), 1922, 2, 253-765.

The respiratory quotient, the basal metabolism, the blood sugar, ketones and CO<sub>2</sub> combining power of the blood and the total nitrogen, sugar and ketones of the urine were determined before and at various intervals after the administration of insulin. Insulin increased the fasting respiratory quotient not only during the first few hours after administration but for at least 3 days after its cessation. Glycosuria, hyperglycemia and ketosis were abolished. Insulin influences protein metabolism markedly; in several subjects a negative nitrogen balance was changed to a positive balance within a comparatively short time. Insulin seems to have only an indirect effect upon basal metabolism.—I. M.

The blood sugar following INSULIN administration and symptom complex-hypoglycemia. Fletcher (A. A.) & Campbell (W. R.), *J. Metab. Research* (Morristown), 1922, 2, 637-649.

The blood sugar was determined before and at hourly intervals after administration of insulin. A fast of 14 hours preceded each

experiment. The blood sugar was lowered in all cases, the lowest level being reached in from 2 to 4 hours after insulin administration. In general the greatest absolute and percentage decreases were found in those cases with the highest initial values. Proportionally greater dosage is required to produce hypoglycemia than to reduce hyperglycemia. In 2 subjects insulin was administered in different amounts on different days. It was found that there is no accurate relationship between insulin dosage and amount of reduction of blood sugar. The symptom complex of hypoglycemia and its treatment are described in detail. The symptoms appear in different subjects at different blood sugar levels, varying from 0.035% to 0.070%. They are at first nervousness, excessive hunger and weakness and later, profuse perspiration, emotional instability, aphasia, confusion, syncope or collapse and finally unconsciousness and convulsions. Adrenalin injection, 1 cc. of 1:1000 solution in severe cases, followed by glucose intravenously or by mouth or glucose alone constitutes the treatment.—I. M.

**The effect of INSULIN on the central nervous system and its relation to the PITUITARY body.** Olmsted (J. M. D.) & Logan (H. D.), *Am. J. Physiol. (Balt.)*, 1923, 66, 437-444.

If the pituitary is left intact in decerebrate cats, the blood sugar is high, and but little affected by insulin. If the pituitary is removed, typical insulin convulsions can be induced. The presence or absence of the adrenals appears not to influence the results. There are no signs of convulsions in decapitate cats even if the blood sugar is maintained at the convulsion level of normal cats. The locus of action of insulin is on the bulbar centers, particularly the respiratory center.—T. C. B.

**The use of insulin in juvenile DIABETES.** Geyelin (H. R.), Harrop (G.), Murray (Marjorie F.) & Corwin (Eugenia), *J. Metab. Research (Morristown)*, 1922, 2, 767-791.

A report of 9 subjects with severe juvenile diabetes treated with insulin over periods of from 3 to 8 months. It was found that the downward course of the disease so well known in juvenile diabetes can be arrested, that steady gain in weight and growth with increase in mental and physical vigor takes place, that a total food intake approximating the normal age requirement in calories can be achieved and that severe or permanent ill effects are not produced by insulin treatment.—I. M.

**Effects following the intestinal administration of (letin) INSULIN.** Hachen (D. S.) & Mills (C. A.), *Am. J. Physiol. (Balt.)*, 1923, 65, 395-402.

Insulin introduced into rabbit intestine promptly lowers the

hyperglycemia due to ether. No effect was noted when large doses were administered by the intestinal route in man.—T. C. B.

The insulin treatment of **DIABETES MELLITUS** in general practice. Hamburger (L. P.), *Internat. Clin. (Phila.)*, 1923, 2, 33s, 21-35.

Insulin will reduce hyperglycemia due to any cause. How insulin acts is still unknown; its effects are probably the result of a promotion of glycogenesis. Five case histories are reported in detail,—2 of them of children,—showing the marked effects of insulin in patients suffering with apparently hopeless cases of diabetes mellitus. For the average case the strength of insulin designated as H10 is advised; this is administered subcutaneously from 15 to 30 minutes before 2 meals. In refractory cases it may be given before each of the 3 meals. Ordinarily 5 units twice a day are administered at the beginning of treatment. Because of the possibility of severe reactions the dosage should be increased cautiously. Mild reactions may be combatted by orange juice, candy, or sugar in any form given by mouth. Severe reactions require intravenous injections of glucose. Insulin properly administered for a long period will so spare the pancreas of diabetics that the function of the organ may be restored either to normal or with slight modification of the diet, to a practically normal status.—I. B.

Insulin and diet in the treatment of **DIABETES**. Harris (S.), *Internat. Clin. (Phila.)*, 1923, 2, 33s, 6-20.

A good general review of insulin therapy. This substance will bear the same relationship to diabetes that thyroid extract bears to hypothyroidism. It is probable that by giving rest to the pancreas in the early stages of diabetes insulin will cure many cases permanently. The use of insulin in diabetic coma is quite as life saving a procedure as the use of antitoxin in severe diphtheritic infection. The use of insulin should be controlled by frequent blood sugar determinations in order to determine the degree of tolerance of the patient in question. The limitations and indications for the use of insulin, as well as the dosage and method of administration are adequately discussed by the author. He warns against certain useless biological products recently placed upon the market. The Wilder modification of Woodyatt's maintenance diet, as used in the Toronto General Hospital, seems to be the best method in the beginning treatment of diabetes. Starting with a diet based on Banting's method of estimating the diabetic's maintenance diet, the patient, becoming clinically improved, is placed on an increased dietary until he is getting 500 calories more than the low maintenance diet, if his blood sugar is about normal. This dietary is continued indefinitely and no insulin is required, the patient increasing markedly in weight and vigor. The dietary of severe diabetics must be managed

somewhat differently, depending upon the progress of the disease and the existence of complications. Relatively large doses of insulin are required in these cases. The question of educating the diabetic to the needs of careful self-observation is vital. Focal infections, too, whether causative or sequentially related to diabetes, require careful attention. In this relation are included especially such conditions as chronic pancreatitis, gall bladder and gastro-intestinal infection. An achylia may be the cause of pancreatic deficiency, and may be improved by the administration to the patient of dilute hydrochloric acid with the food. Harris believes that a rest in bed at the beginning of treatment is useful and should depend for its duration on the physical condition of the patient. Since emotional excitement may bring on a severe and even fatal hyperglycemia, the author regards an attitude of serenity of mind as important.—I. B.

**DIABETES; deaths following sudden changes in diet.** Joslin (E. P.), *Med. Clin. N. Am. (Phila.)*, 1922, 5, 1205-1212.

A discourse on the value of dietary vigilance in the treatment of diabetes mellitus, with illustrative cases. Sudden death in diabetes may take place because of (1) inanition, particularly when the blood sugar falls far below the normal level; (2) heart disease, especially angina pectoris; and (3) diabetic coma, the most common cause of death. Formerly two-thirds of all the author's fatal cases succumbed to coma, but among the 536 diabetics treated in hospitals since April 1, 1919, there were but 4 instances among 16 deaths, and another case complicated with pregnancy and pneumonia. About 90% of cases of diabetes mellitus which prove fatal during the first year die of coma. During the first year, however, the disease is most amenable to proper treatment.—I. B.

**DIABETES of five years' duration in a fifteen-year-old boy.** Joslin (E. P.), *Med. Clin. N. Am. (Phila.)*, 1922, 5, 1212-1220.

A boy, aged 15, during 5 years of treatment for diabetes mellitus, was under hospital observation on 8 different occasions. Despite faithful and intelligent co-operation on the part of the patient, the disease became more severe. Following the institution of the Burgh-Marsh high-fat dietary, the urinary and blood sugar still remained above normal, but the boy's general condition seemed improved and he was sent home. Eighteen days later he returned feeling much better, the urine was free from sugar and diacetic acid; blood sugar was 0.08%, blood fat, 0.70%, and there was a gain of 5 pounds in weight.—I. B.

**INSULIN in hospital and home.** Joslin (E. P.), Gray (H.) & Root (H. F.), *J. Metab. Research (Morristown)*, 1922, 2, 651-699.

A comprehensive report of 83 subjects with diabetes mellitus treated with insulin between August 7, 1922, and January 25, 1923.



The necessity for special education on the part of the patient receiving insulin is emphasized. Of the 83 patients with severe cases treated with insulin 78 are still alive, have shown improvement and are able to take about one-third larger diet with than without insulin, although the dosage is relatively small in most cases. Death was caused in 2 patients by severe lobar pneumonia, in 1, by tuberculosis and hepatic cirrhosis, and in the other 2 by coma. Ketones were abolished from the urine and the  $\text{CO}_2$  combining power of the blood was elevated in all cases of acidosis except in the fatal cases in which too small doses of insulin may have been used. The authors do not consider it necessary to maintain the fasting blood sugar at the normal level, but the average blood sugar value in their patients was reduced from 0.24 to 0.19%. The average gain in weight was 2.6 kg. or 7.6%. Patients from 2 to 77 years responded equally well to treatment, as did subjects with cases of short and long duration. Diarrhea or other complications producing a lessened blood volume was found to be a factor favoring the development of hypoglycemic reactions. The basal metabolism increased with the use of insulin and the respiratory quotient rose with food after insulin to above unity. By improving the diabetic condition insulin aided in the recovery from both local and generalized infection. The ineffectiveness of insulin by mouth, even in enormous dosages, was demonstrated. Properly trained patients were able to continue treatment at home satisfactorily.—I. M.

**DIABETES statistics.** Kaas (J.), *Bibliot. f. Læger* (Copenhagen), 1921, 113, 133-150; 273-279.

According to statistics in Denmark from 1890 to 1916 there has been an increase of deaths from diabetes. After examination of conditions in a little town in which there was a large number of cases the author concluded that bad hygienic conditions rather than heredity was the primary cause of diabetes; he also thinks that some cases might be of infectious origin. Some cases have been found in the literature supporting this view. During the war the Danish population was on a ration. Patients with diabetes could obtain an extra portion of butter and bacon upon medical prescription. The author collected these prescriptions and studied the distribution of the cases. The number of cases in men increased up to the age of 65-69, in women up to 70-74. Among 1028 patients there were 618 men and 410 women. Heredity was found to be a factor in 20% of the cases. In Copenhagen (about 600,000 inhabitants) there were about 2000 diabetics.—K. H. K.

**Treatment of DIABETES with insulin** (*Traitement du diabète par l'insuline*). Labbé (M.), *Bull. et mém. Soc. méd. d. hôp. d. Par.*, 1923, 47, 1051-1058.

The majority of diabetics need no treatment with insulin. It is in the severe progressive cases, in which nitrogenous waste and acidosis occur, tending to coma, that insulin treatment is of benefit. The insulin prepared in France is less active than is that made in either America or Great Britain.—F. S. H.

Acidosis in **DIABETES** and elsewhere (*L'acidose dans le diabète, et en dehors du diabète*). Labbé (M.), *Rev. méd. d. Rosario*, 1921-22, 11, 207-218.

Ketosis is observed in diabetes, in the vomiting of pregnancy, dyspeptic coma, etc. This is a symptom of liver insufficiency. Diabetic coma may be due to ketogenic acids or to certain derivations of protein metabolism.—B. A. H.

**Familial DIABETES.** Landis (H. R. M.), *Tr. Ass. Am. Physicians* (Phila.), 1921, 36, 293-295.

In a woman of 58 the persistent presence of sugar in the urine was observed. Urinary examination of the patient's brothers and sisters led to the discovery that the 5 brunettes of the family were diabetic, while the 4 blondes were free from glycosuria. There was a history of tuberculosis in 3 of the 4 generations investigated by the author.—I. B.

The treatment of **DIABETES MELLITUS** with insulin. Major (R. H.), *J. Am. M. Ass. (Chicago)*, 1923, 80, 1597-1600.

Major confirms the value of insulin treatment in a series of 30 subjects, 7 being described briefly. In one case of severe juvenile diabetes and several cases of impending coma the results were striking. One patient in complete coma responded after receiving 130 units in 24 hours. Lipemia also disappears under insulin therapy.  
—W. M. A.

The effect of **INSULIN** on the blood sugar following total and partial removal of the liver. Mann (F. C.) & Magath (T. B.), *Am. J. Physiol. (Balt.)*, 1923, 65, 403-417.

The symptoms associated with the hypoglycemia following administration of insulin are practically the same as those following removal of the liver, but the hypoglycemia following insulin may not be associated with symptoms, while that following removal of the liver always is. The experiments show that the liver is certainly not necessary for the hypoglycemic action of insulin, but they do not show that it is not involved in such action.—T. C. B.

**Insulin in the treatment of severe DIABETES.** McPhedran (A.) & Banting (F. G.), *Internat. Clin. (Phila.)*, 1923, 2, 33s, 1-5.

A case of diabetes mellitus is considered severe when the patient is unable to metabolize 500 calories over and above the basal needs

One must first know the tolerance of the patient to insulin. In a moderately severe diabetic patient one unit of insulin is capable of burning 2.5 gm. of glucose. In milder cases the utilization per unit is greater, while in instances complicated by infection with fever it is less. The practical points of insulin treatment mentioned in this paper must be read in the original to be fully appreciated. Insulin is not a cure, but a treatment for diabetes. It enables the patient to burn sufficient carbohydrate so that proteins and fats may be added to the diet in sufficient quantities to provide energy for the economic burdens of life.—I. B.

The influence of neutral or alkaline perfusates on the respiratory metabolism of **DEPANCREATIZED** animals. Murlin (J. R.), Clough (H. D.) & Stokes (A. M.), *Am. J. Physiol. (Balt.)*, 1923, 64, 330-347.

Weakly alkaline Ringer-Locke's solution extracted from the pancreas in small amount a substance capable of increasing the respiratory quotient in the depancreatized dog or cat.—*Physiol. Abst.*, 8, 168.

Observations on the use of insulin in **DIABETES MELLITUS**. Olmsted (W. H.) & Kahn (S. H.), *J. Am. M. Ass. (Chicago)*, 1923, 80, 1903-1907.

With the aid of a number of charts and tables Olmsted and Kahn report observations on a series of over 40 cases of severe diabetes treated with insulin. They find favorable effect on hyperglycemia, glycosuria, acetonuria, nitrogen balance, basal metabolic rate, blood alkali and general symptoms. Insulin preserves carbohydrate tolerance but the authors are not sure as yet that it increases it.—*W. M. A.*

Influence of sugars and other substances on the toxic effects of **INSULIN**. Noble (E. C.) & Macleod (J. J. R.), *Am. J. Physiol. (Balt.)*, 1923, 64, 547-560.

"The only sugar which can definitely antidote the symptoms that accompany the hypoglycemia due to insulin is glucose. Even when the animal is moribund at the time of injection this sugar may bring about permanent recovery."—*T. C. B.*

The influence of diet on the alkaline reserve and **INSULIN** hypoglycemia in rabbits. Page (I. H.), *Am. J. Physiol. (Balt.)*, 1923, 66, 1-4.

A fall in alkali reserve is associated with hyperglycemia; any factor tending to produce such a fall should render the animal more resistant to hypoglycemia. The present investigation shows diet to

be such a factor. Rabbits kept on an acid forming diet are more resistant to insulin hypoglycemia than those kept on basic diets.

—T. C. B.

**The practical use of insulin in the treatment of DIABETES.** Petty (O. H.), *Internat. Clin. (Phila.)*, 1923, 2, 33s., 37-59.

Insulin rapidly lowers the hyperglycemia of diabetes mellitus, raises the respiratory quotient, renders the urine free from sugar, acetone and diacetic acid, and, if administered in sufficient amount with proper dietary instructions, will increase the patient's weight and restore to normal his physical, mental and reproductive powers. Insulin is not a cure for diabetes but is a therapeutic measure of extreme value. In Petty's experience, the average amount of carbohydrates controlled by one unit of insulin is 1.5 gms. Since this is subject to many variations, each patient must be tried out with diet, blood sugar tests and insulin before the dosage of the latter can be decided upon. A thorough knowledge of the dietetic management of diabetes mellitus is a vital prerequisite to the use of insulin; this applies both to physician and patient. Among the cases cited by the author are 6 of coma and 4 of impending coma in which the patients were drowsy, blood sugars were above 280 mgs., and there were marked urinary diacetic and acetone reactions. All 4 patients with impending coma recovered; one of the subjects in coma died, making the percentage of recovery in the coma cases approximately 83. The response to insulin in children, especially in severe cases of diabetes mellitus, is almost miraculous. The overdose of insulin is not difficult to detect but can be determined with mathematical precision by blood chemistry and corrected within a short while by the oral or intravenous administration of a few grams of glucose.

—I. B.

**The effect of INSULIN upon morphine hyperglycemia.** Stewart (G. N.) & Rogoff (J. M.), *Am. J. Physiol. (Balt.)*, 1923, 65, 331-341.

Morphine hyperglycemia is counteracted by insulin, just as is other experimental hyperglycemias in which the adrenals are not essential.—T. C. B.

**Fats in the treatment of DIABETES.** Strouse (S.), *Med. Clin. N. Am. (Phila.)*, 1921, 5, 233-237.

A brief discourse on the value of a high fat dietary in the treatment of diabetes mellitus. Case histories of 2 patients are detailed; in each there was complete disappearance of acidosis and marked general improvement under this dietary.—I. B.

**Mild DIABETES MELLITUS with acute and chronic cholecystitis.** Strouse (S.), *Med. Clin. N. Am. (Phila.)*, 1921, 5, 237-238.

A man aged 46, with diabetes mellitus of long standing and an apparently serious gall bladder infection, was placed on a protein 50, carbohydrate 50 and fat 50 dietary for 4 days. He became sugar and acetone free and the gall bladder symptoms subsided. Ten days after admission to the hospital the diet was changed to protein 20, fat 136 and carbohydrate 25. When the patient left the hospital he was on a dietary of protein 100, fat 140 and carbohydrate 55. He was free from acetone and sugar and in excellent condition.—I. B.

**Severe DIABETES MELLITUS, pulmonary abscess, and hemopneumothorax.** Strouse (S.), *Med. Clin. N. Am. (Phila.)*, 1921, 5, 239-241.

A woman of 29 entered the hospital complaining of cough, vomiting, weakness, and loss of weight. There had been gradually increasing weakness and dyspnea for 2 months prior to this time. There was a loss of 81 pounds in weight during the past year, the period during which she was conscious of the presence of diabetes. On physical examination the patient appeared desperately ill, with marked dyspnea, cyanosis, cough, high fever, and an acetone odor to the breath. The chest examination revealed the presence of pulmonary abscess on the right side and hemopneumothorax. The blood sugar was 0.80%. The urine showed a specific gravity of 1040 with 3.75% sugar; acetone and diacetic acid were also present. Following a preliminary dietary to overcome acidosis she was put on a high fat dietary, 3 days after the institution of which she became sugar and acetone free, and her blood sugar was reduced to 0.17. Despite the fact that there still persisted the signs and symptoms of pulmonary abscess, her urine remained sugar free and her general condition was greatly improved. The author concludes that the patient would not have improved on any but a high fat dietary.

—I. B.

**Insulin in DIABETES complicated by infection: Necropsy reports of three fatal cases.** Strouse (S.) & Schultz (O. T.), *J. Am. M. Ass. (Chicago)*, 1923, 80, 1592-1596.

In 2 patients with localized infection insulin therapy gave striking benefit; in the 3 fatal cases the pathologic findings were so extensive that little could be expected of insulin.—W. M. A.

**Influence of PANCREAS extract on diabetes mellitus. (Experimentelle Untersuchungen über die Beeinflussung des Diabetes mellitus durch Pankreasextrakte).** Stuber (B.) & Krastel (A. R.), *Biochem. Ztschr. (Berl.)*, 1923, 138, 56-71.

Freshly extirpated pancreas was freed from fat and connective tissue as much as possible and ground up with sand. It was then macerated with methyl alcohol in the shaking machine. The mass

was then extracted with methyl alcohol containing 2% sulfuric acid for 8 hours using a reflux condenser. The filtrate was treated with 10% phosphotungstic acid until no further precipitate was formed. After standing for 24 hours the precipitate was digested in a water solution of barium hydroxide and filtered after 12 hours. The filtrate was neutralized with sulfuric acid and tested on depancreatized dogs, and rabbits made glucosuric with adrenin. A silver fractionation was also made of the precipitated compounds. The injection of extracts so prepared caused lowering of the blood-sugar values. The anti-diabetic action reached its maximum point some 15 to 20 minutes after the administration and then receded rather rapidly so that after 2 or 3 hours the blood sugar reached again its former point. Sugar excretion was also lowered. The adrenin glycosuria was shortened and in one case inhibited.—F. S. H.

**Diminished glycolysis in the blood in DIABETES.** Preliminary report and a tentative theory of the disease. Thalhimer (W.) & Perry (Margaret C.), J. Am. M. Ass. (Chicago), 1923, 80, 1614-1616.

The loss of blood sugar in sterile defibrinated blood, incubated at 37° C. for 24 hours, has been studied by Thalhimer and Perry in a series of 9 diabetic and 6 normal subjects. Glycolysis was diminished in diabetic blood in proportion to the severity of the disease. Lactic acid was demonstrated in the blood at the end of incubation. Fresh sterile potato juice reduced the blood sugar level in a rabbit and caused glycolysis in vitro. As a result of their own and other recent work the authors advance the theory that diabetes is caused by a deficiency in the oxidizing ferments in all tissues, and that these ferments are stimulated or activated by a pancreatic hormone.

—W. M. A.

**Rarity of DIABETES MELLITUS in Croatia** (Ueber die Seltenheit des Diabetes mellitus in Kroatien). Thaller (L.), Wien. med. Wchnschr., 1923, 36, 541.

In Croatia the author treated in 10 years 22,792 patients. Only 26 suffered from diabetes and only 1 died in coma.—J. K.

**On the effect of INSULIN on blood phosphate.** Wigglesworth (V. B.), Woodrow (C. E.), Smith (W.) & Winter (L. B.), J. Physiol. (Lond.), 1923, 37, 447-449.

Injection of insulin in rabbits causes a rapid fall in inorganic phosphorus, which is maintained many hours after recovery from convulsions. The total acid-soluble phosphorus is very little altered.

—T. C. B.

**Clinical observations on INSULIN.** Wilder (R. M.), Boothby (W. M.), Barborka (C. J.), Kitchen (H. D.) & Adams (S. F.), J. Metab. Research (Morristown), 1922, 2, 701-728.

The glucose tolerance of patients with uncomplicated diabetes is determined under standard dietetic conditions without insulin. Then, a dosage of insulin (20 to 40 units) is administered, thus permitting an increase of the daily diet to a standard food mixture of about 2500 calories. The tolerance on this diet with insulin, minus the original or basal tolerance without it, gives the grams of glucose utilized by the body with the help of the insulin only, and this, divided by the number of units employed, gives the glucose value of each unit of insulin. The diet is made up in both cases with 0.67 gm. of protein per kilo body weight and with carbohydrate and fat so adjusted as to safely guard against ketogenesis. The 24 hour urine is allowed to contain a trace of glucose in both cases. In calculating the total glucose in the metabolism the ingested protein is disregarded and the sugar from the protein sources is determined by multiplying the number of grams of nitrogen in the urine by the factor 3.7. One-tenth of the fat and all of the carbohydrate are calculated as glucose. The basal tolerance is the difference between the glucose value of the standard food mixture and the average daily glucose excretion. As a rule, one rabbit unit of iletin will account for the utilization of 1.5 to 2.0 gm. of glucose in the body. In the clinical use of insulin the results reported confirm those of the Toronto workers. It was found, however, that a single daily dose in the morning was preferable in every way to giving the same quantity in divided doses throughout the day. The mechanism of carbohydrate metabolism is briefly discussed. Fructose, in most instances, is more active in the metabolism with and without insulin than glucose, which suggests that it might be nearer the final form in which glucose is utilized by the body.—I. M.

**A clinical study of the effects of insulin in severe DIABETES.** Williams (J. R.), J. Metab. Research (Morristown), 1922, 2, 729-751.

The author reports the results of the insulin treatment of 44 subjects with severe diabetes and compares them with the results of careful dietetic management, alone, on the same patients and 56 others. During the periods of observations—20 to 250 days—only 4 patients died, 2 from coma because of insufficient insulin supply and 2 from causes other than diabetes. Insulin treatment brought about far greater comfort and strength in the 40 living subjects than had before been experienced. The attempt to utilize high diets by large doses of insulin was not found to be satisfactory. More satisfactory results were obtained if the insulin was given in several doses throughout the day rather than the same amount in

one dose. Insulin first caused storage of glucose, then release from the tissues into the blood stream. No definite influence was observed on the natural function of the pancreas.—I. M.

On the lowering of the blood sugar by an extract of yeast. Winter (L. B.) & Smith (W.), *J. Physiol. (Lond.)*, 1923, 57, xl.

A solid preparation has been obtained from yeast which appears to be similar to "insulin" in its properties and effects—e. g., lowering of blood sugar, production of convulsions. Both contain P and carbohydrate. Seliwanoff's reaction is positive in each case after hydrolysis.—*Physiol. Abst.*, 8, 111.

An effect of INSULIN on the nature of the blood sugar. Winter (L. B.) & Smith (W.), *J. Physiol. (Lond.)*, 1923, 57, lxx.

Following injection of insulin into normal rabbits, the copper reducing power becomes gradually lower, and when the animal is nearing or in convulsions, is quite absent. The average blood sugar by Bang's method at this state is 0.05%. The blood filtrate contains a dextro-rotatory substance of a carbohydrate nature.—*Physiol. Abst.*, 8, 252.

The clinical use of INSULIN. Woodyatt (R. T.), *J. Metab. Research (Morristown)*, 1922, 2, 793-801.

A summary of the results of the insulin treatment of 150 diabetic patients. The author concludes that the subcutaneous or intravenous routes of administration are the most convenient and reliable. One dose daily was satisfactory in 90% of the subjects; division into 2 injections was necessary in exceptional cases only. The dosage and the method of insulin treatment should be determined for the individual patient. In general, a certain diet approximately fulfilling basal requirement is given. If desugarization occurs the diet is increased until glycosuria occurs. Unless the diet is a proper one for the subject without causing glycosuria, enough insulin is given to supplement the natural powers of the patient to metabolize it almost completely. For the assay of insulin subjects with long-standing diabetes with well-known food tolerance were given diets which would allow the excretion of 20 to 25 gm. glucose per day. A certain number of units of insulin (about 10) were then given and the amount of glycosuria again determined. The difference between the two 24 hour amounts of sugar excreted divided by the number of units of insulin given gives the carbohydrate equivalent of the insulin unit; this is between 1 and 1.5 gm. glucose per 1 rabbit unit. The author has used insulin temporarily in some subjects to desugarize and restore tolerance in order to save time for the patient and to spare the hardship of a week or so of under-nutrition. Withdrawal of the insulin left the patient still on his diet without glycosuria. Since the author found renal glycosuria to be



unaffected by insulin he suggests its use in questionable cases as a diagnostic test. It is unnecessary for the subject to be kept sugar free in very advanced cases because there is no natural tolerance to lose, whereas it is desirable for those with considerable natural tolerance or power to regain such.—I. M.

*Interrelation between PARATHYROID function and intestinal secretion* (Sulle correlazioni tra funzione paratiroidica e secrezione enterica). Artom (C.), *Riforma med.* (Napoli), 1922, **38**, 856.

Following removal of the thyroid and parathyroids there is progressive diminution in the amount of intestinal secretion as well as of its invertase and erepsin content; if the thyroid alone is removed no change is seen. After partial parathyroidectomy the same phenomenon is temporarily observed. Calcium salts seem to be of value even for the enteric condition in parathyroid insufficiency.  
—G. V.

*The pathogenesis of PARATHYROID tetany.* Dragstedt (L. R.), *J. Am. M. Ass.* (Chicago), 1922, **79**, 1593-1594.

As a result of a series of experiments on 32 dogs, Dragstedt concludes that parathyroid tetany is due to an intoxication; the toxic substances come from the gastro-intestinal tract. They arise through the activity of the proteolytic group of bacteria and are probably of the nature of amines. The function of the parathyroid glands is to prevent intoxication by these poisons. The parathyroids do not furnish a hormone necessary for life, and dogs may be kept alive indefinitely if treatment is directed to the prevention of this toxemia.—W. M. A.

*The control and cure of PARATHYROID tetany by diet.* Dragstedt (L. R.) & Peacock (S. C.), *Am. J. Physiol.* (Balt.), 1923, **64**, 424-434; see also *ibid.*, **63**, 408-409 (Proc.).

Parathyroid tetany is due to an intoxication by the products of proteolytic bacteria, and it is the function of these glands to prevent intoxication by these poisons. The parathyroids do not furnish a hormone necessary for life.—T. C. B.

*The mechanism involved in recovery from PARATHYROID tetany.* Dragstedt (L. R.), Phillips (K.) & Sudan (A. C.), *Am. J. Physiol.* (Balt.), 1923, **65**, 368-378.

Having previously shown that parathyroidectomized dogs can be kept alive indefinitely by a special carbohydrate diet, experiments were made with various substances to determine the mechanism. It was found that parathyroidectomized dogs were less resistant to guanidine, methylguanidine, trimethylamine, histamine and intestinal poisons, than were normal dogs, and doses that have no effect in normal dogs may produce symptoms of tetany in parathyroidecto-

mized dogs. It is suggested that the parathyroids form part of a detoxicating mechanism of the body.—T. C. B.

(PARATHYROID) Exciting factors in experimental tetany in dogs. Dragstedt (L. R.), Phillips (K.) & Sudan (A. C.), *Am. J. Physiol.* (Balt.), 1923, 65, 503-511.

Protocols of various experiments to show that tetany is due to infection. Tetany can be induced in parathyroidectomized dogs that have been kept in good condition by a carbohydrate diet by various conditions, such as feeding meat, high temperature, muscular exercise, estrus and infection. It is suggested that tetany in man may be the result of relative insufficiency of the detoxicating mechanism of the parathyroids, without a lesion of these glands.—T. C. B.

The direct influence of the blood of PARATHYROID tetany animals on the excitability of the motor nerves. Jacobson (Clara), *Am. J. Physiol.* (Balt.), 1923, 63, 535-539.

There is a chemical change in the blood directly affecting excitability of nerve. The experiments were made by cross circulation between a dog with tetany and a normal dog.—*Physiol. Abst.*, 8, 141.

The influence of PINEAL and TESTICLE substance on the growth and development of tadpoles (*Der Einfluss der Zirbeldrüsen und Hodensubstanz auf Wachstum und Entwicklung von Froschlärven*). Groebels (F.) & Kuhn (E.), *Ztschr. f. Biol.* (München. u. Leipz.), 1923, 78, 1-6.

Acceleration of development and increase of growth occurs after feeding with pineal and testicle substance. Addition of testicle substance to insufficiently fed larvae makes up for the lack of growth.—*Physiol. Abst.*, 8, 232.

PINEAL tumors and cerebral adiposity (*Zur Diagnostik der Zirbelgeschwülste und zur Kritik der cerebralen Adipositas*). Luce (H.), *Deutsche Ztschr. f. Nervenhe.* (Leipz.), 1921, 68/69, 137-210.

In a child of 5½ years partial ophthalmoplegia and cerebellar ataxia were noted. The roentgenogram showed the shadow of a calcified pineal gland. There was also hydrocephalus and slight adiposity. A case is reported of angiosarcoma at the base of the brain in the region of the pons and base of the mesencephalon. Macroscopically and microscopically the pituitary was intact. There were considerable adiposity, amenorrhea, symptoms of cerebral tumor and hyperglycemia (0.21%). The author concludes that internal hydrocephalus may cause dystrophia adiposogenitalis by mechanical or toxic irritation of the mesencephalic centers and that there is no specific pituitary or pineal adiposity. Pineal tumors may cause adiposity by direct pressure upon the mesencephalic cen-

ters by producing hydrocephalus or by toxic influence upon the centers. Precocious development in cases of pineal tumor is the consequence of absence of the inhibitory pineal hormone and of an unusually large amount of sexual hormones.—A. B.

**Rhythmical convergence spasm of the eyes in a case of tumor of the PINEAL gland.** de Monchy (S. J. R.), Brain (Lond.), 1923, 46, 179-188.

The tumor, a teratoma, in a boy of 14, consisted of two parts, joined by connective tissue, one lying in the situation of the pineal, the other between the folds of the dura mater where the falx cerebri and tentorium cerebelli meet. The Argyll-Robertson sign was present, with lymphocytosis of the cerebro-spinal fluid, not due to cerebro-spinal syphilis. The general picture was similar to that in dystrophia adiposogenitalis.—A. T. C.

**Relations between defective diet and the THYMUS gland in tadpoles of *Rana temporaria*** (Die Beziehungen zwischen unzureichender Ernährung und Thymuswirkung bei Larven von *Rana temporaria*). Groebbels (F.), Ztschr. f. Biol. (München), 1922, 77, 249-260.

Young tadpoles fed on calves' thymus, either the gland, or an extract of it, gain weight faster than controls. They retain their larval appearance and are marked by a general deep pigmentation of the skin. Older tadpoles, however, gain weight less rapidly than normal animals. Vitamine free "Pisididin" was used as a defective diet. Older animals fed this alone show, usually, an increased rate of development and always a decrease in gain of weight compared with controls. These animals soon become very light in color. If, however, the animals are less than 3 weeks old at the start, the defectively nourished animals gain weight faster than the normal. When thymus is added to the above diet the tadpoles develop the typical thymus effects in weight and color as seen in the first experiments. These effects are slower to appear than in the normally nourished thymus fed larvae. The development of the defectively fed animals whether thymus is added or not is more rapid than normal and proceeds at about the same rate in the two cases. Autoclaved thymus extract produces a relative increase in weight in normally fed tadpoles, but this result decreases with time. It produces a marked retardation in development both in normal and vitamine starved tadpoles.—J. C. D.

**The effects of THYMECTOMY** (Sugli effetti della timectomia). Pighini (G.), Riv. sper. di freniat. (Reggio Emilia), 1922, 46, 1-88.

Whenever thymectomy is performed at the proper time (the first 14 days in dogs, the first months of life in chickens) patho-

logical changes, in Pighini's experience, invariably follow. After a certain stage of development thymectomy does not bring about such regular and striking consequences. Lesions are found in the organism in the following order: bones, chromaffine tissue, neuromuscular system, hemolymphatic system (blood and spleen), sexual glands, thyroid, pancreas, liver and adrenal cortex. Man seems to be even more sensitive than animals to thymectomy. In the early extrauterine life, before puberty, the thymus is indispensable. Its removal at such a time causes abnormal conditions in nearly all tissues and organs, leading to death with clinical symptoms of progressive cachexia and mental weakness. The amount and the frequency of the lesions vary according to the peculiar metabolism and constitution of the subject. The incidence of lesions is as follows: bones, chromaffine cells, neuromuscular system, hemolymphatic system (blood and spleen), male sexual glands, adrenal cortex, female sexual glands, pancreas and liver, thyroid and hypophysis. The thymus has a trophic as well as an evolutive action, especially on bones, lymphatic system, sexual glands and central nervous system. Through lesion of the thymus the nuclein metabolism of the organism becomes altered. The thymus has a great deal of influence on the calcium metabolism also. The hypocalcification of bones following thymectomy perhaps is not due to acid poisoning, but to the lack in the circulation of ferments, hormones or other specific substances, so that activity of the osteoblasts and morphologic evolution of the epiphyseal cartilages is inhibited.—G. V.

Behavior of **THYROIDLESS** and normal guinea-pigs with a scorbutic diet (*Vergleichende Versuche über das Verhalten von schilddrüsenlosen Meerschweinchen und solchen, die Schilddrüsen besitzen, gegenüber einer Nahrung, die zum Skorbut führt*). Abderhalden (E.), *Arch. f. d. ges. Physiol. (Berl.)*, 1923, 198, 164-168.

Thyroidless animals suffered more severely from scurvy, though its onset was not earlier than usual.—A. T. C.

Behavior of the active principle of the **THYROID** gland in the animal body (*Über das Verhalten der wirksamen Schilddrüsenstoffe im tierischen Organismus*). Abelin (J.), *Biochem. Ztschr. (Berl.)*, 1923, 138, 169-175.

Four white rats were fed for one week with large amounts of an active thyroid preparation. This substance which normally affects the metamorphosis of frog larvae could not be detected in the blood, the urine or the liver, spleen, kidneys or brain. No iodine could be found in the liver of thyroid-fed rats.—F. S. H.

The relation of acromegaly to **THYROID** disease: a statistical study.

Anders (J. M.) & Jameson (H. L.), *Am. J. M. Sc. (Phila.)*, 1922, 163, 190-211.

The authors record 2 cases illustrating modifications of the functions of the thyroid in acromegaly, and have compiled tables showing that among 215 cases of acromegaly on record lesions of the pituitary are mentioned in 99, and in 68 cases thyroid changes are described. They think it highly probable that in many cases of pituitary disease with its usual syndrome the coexistence of thyroid alterations and symptoms resulting therefrom was overlooked. Hypothyroidism was found to be more commonly associated with acromegaly than hyperthyroidism, and combined cases with myxedematous features were decidedly improved by thyroid preparations. The writers emphasize the fact that recognition of hypothyroidism in acromegaly is most important, and recommend that the metabolic rate should be determined in cases of acromegaly which present features suggestive of hypo- or hyper-thyroidism.—*Med. Sc.*, 8, 293.

Modifications in the lipid content of the liver after **THYROID-ECTOMY** (*Sulle modificazioni del contenuto in lipoidi nel fegato dopo tiroidectomia*). Artom (G.), *Riforma med. (Napoli)*, 1922, 38, 596.

After thyroidectomy the phosphatic fatty acids are diminished while the glycerids are increased. There is also a change of relation between phosphatic fatty acids and total acidity and between cholesterin and phosphatic fatty acids.—*G. V.*

Vitiligo and alopecia areata with severe **HYPERTHYROIDISM**.

Ayres (S.), *Arch. de dermat. et syph.*, 1923, 8, 502.

The author cites a case of vitiligo and alopecia areata occurring in the same patient. There was a symmetrical enlargement over the thyroid area, tachycardia, tremor of the extended fingers and profuse sweating. The basal metabolic rate was 53.9.—*L. K. McC.*

The simultaneous occurrence of tumors in the **THYROID**, uterus and breast. Ballin (M.) & Moehlig (R. C.), *J. Am. M. Ass. (Chicago)*, 1922, 79, 1243-1244.

In a series of 100 cases of goiter 18 subjects had fibroids of the uterus and 4 had breast tumors; and in a series of 100 cases of fibroids of the uterus, 35 patients had goiter and 6 had breast tumors. Thus, of the total 26.5% had tumors of both thyroid and uterus and 5% had breast tumors; this Ballin and Moehlig conclude is in some way the result of the physiological connection of these organs.—*W. M. A.*

Tonsil **THYROID** syndrome in the female (preliminary report).

Barach (J. H.), *N. York M. J. [etc.]*, 1921, 114, 648-649.

In a paper based on the study of 25 cases, Barach describes a syndrome in females aged from 15 to 35 in whom, as the result of chronic tonsillar infection, a clinical picture of hypothyroidism develops.—Med. Sc., 8, 290.

**(THYROID)** The study of vestibular nerve function in myxedema.

Barlow (R. A.), Am. J. M. Sc. (Phila.), 1922, 164, 401-414.

As the result of the study of 15 cases of myxedema, Barlow came to the conclusion that there is in this disease a definite clinical vestibular picture which can be demonstrated by equilibration tests, and is in the nature of a delayed response to stimuli. There was no relation between the basal metabolic rate and the degree of the retardation.—Med. Sc., 8, 289.

**Influence of ovary extract on GOITER** (Beeinflussung von Strumen durch Ovarialextrakt). Bauer (R.), Wien. klin. Wchnschr., 1923, 30, 416.

Description of 4 patients in whom the goiter became smaller after injections of ovoglandol.—J. K.

**Cardiac disorders accompanying exophthalmic GOITER.** Boas (E. P.), J. Am. M. Ass. (Chicago), 1923, 80, 1683-1684.

Boas calls attention to 2 mechanical factors existing in exophthalmic goiter which may largely account for the cardiac disorders so frequently found, viz., (1) the great dilation of the thyroid arteries and veins amounting almost to an arterio-venous fistula, and (2) the necessity for greater exchange of oxygen and carbon dioxide because of the elevated metabolism. Both of these factors throw increased work on the heart which, acting over a long period of time, lead to hypertrophy and other disorders. Metabolic data on 55 cases are presented in support of the second supposition.

—W. M. A.

**A preliminary note on the food requirement in HYPERTHYROIDISM.** Boothby (W. M.) & Sandiford (Irene), Med. Clin. N. Am. (Phila.), 1921, 5, 425-429.

General deductions drawn from a detailed study of the food requirements of 2 patients with hyperthyroidism, the basal metabolism of whom was 40 and 50%, respectively, above normal. Subjects of hyperthyroidism require while at rest in bed even more calories than men doing hard work, or about the same as 2 patients without hyperthyroidism. These patients likewise require large quantities of water. The natural desire for large quantities of food despite persistent loss of weight is a valuable diagnostic sign of hyperthyroidism.—I. B.

(**THYROID**) Two cases of myxedema with glycosuria (*Deux cas de myxœdème avec glycosurie*). Boudot (R.), *Thèses de Par.*, 1921-22, 467.

According to Boudot, who records 2 personal cases of myxedema associated with glycosuria; and has collected 5 others from the literature, cases of myxedema may occur in which the coefficient of assimilation of sugar is lowered. The result is alimentary glycosuria, spontaneous glycosuria, or even true diabetes. The cause of this is to be found in disturbance of the glycemie regulation produced by thyroid insufficiency in other endocrine glands. Treatment by thyroid extract causes the glycosuria to disappear, or at least to diminish in amount.—*Med. Sc.*, 8, 289.

**Exophthalmic GOITER:** the problem of recovery. Bram (I.), *Med. Rec. (N. Y.)*, 1922, 101, 571-575.

In a paper based on a prolonged study of Graves' disease, with a record of over 400 non-surgical recoveries, Bram comes to the conclusion that after exclusion of the moribund, the insane, and the non-coöperative, who constitute about 10% of the patients who apply for advice, non-surgical treatment should produce a cure in 100% of the cases.—*Med. Sc.*, 8, 288.

**Medical treatment of congenital familial GOITER** (*Consideraciones sobre una observación de bocco congénito familiar tratado médicamente*). Bravo & Frias (J.), *Siglo. méd. (Madrid)*, 1922, 69, 225-229.

According to Bravo and Frias, who record 5 cases in a family of 10 children, congenital goiter is uncommon even in countries where goiter is endemic, although numerous examples are on record, not only in man, but also in animals, especially dogs, calves, and goats. The present cases are of special interest, as the subjects came from a part of Spain in which goiter was not endemic, and there was no history of goiter on the father's or mother's side. Thyroid treatment not only improved the symptoms of hypothyroidism, but also had a curative effect on the thyroid lesions, as the goiters diminished considerably in size. The prognosis, therefore, was favorable, though as a rule congenital goiter is a serious affection. Of 32 cases collected by Richards, 2 died at birth and 21 a few days later, 7 recovered spontaneously, and 2 were treated by exothyropexy.—*Med. So.*, 8, 284.

**A case of acute THYROIDITIS.** Bullowa (J. G. M.), *Med. Clin. N. Am. (Phila.)*, 1922, 5, 1125-1128.

A man, aged 31, 5 days after traumatism of the neck, complained of pain and swelling of the throat, dysphonia, extreme dysphagia, repeated chills, and fever. The thyroid gland was swollen

and tender. The temperature varied between 102° and 104° F.; the leucocyte count was 17,000. After 4 days of palliative treatment the condition subsided and the patient left the hospital.—I. B.

New evidence of THYROID secretion following stimulation of the cervical sympathetic. Cannon (W. B.) & Smith (P. E.), Tr. Ass. Am. Physicians (Phila.), 1921, 36, 382.

These are the authors' deductions in abstract form; they do not permit of further condensation. Gentle massage of the thyroid gland in the cat for 2 or 3 minutes will cause an increased rate of the denervated heart, amounting in some instances to 33% over the basal rate. The development of the maximal increase of rate is usually slow, requiring from 30 to 60 minutes, and passing off in a similarly slow manner. Massage of another gland, e. g., the submaxillary, does not cause this effect. The augmentation of heart-rate caused by thyroid massage occurs in the absence of the adrenal glands. Stimulation of the cervical sympathetic trunk as it leaves the stellate ganglion induces a similar augmentation of the rate of the denervated heart; this does not occur if the thyroid gland has previously been removed. If the cardiac fibers from the stellate ganglia are severed, as well as the vagus nerves, and an afferent nerve, such as the sciatic or brachial, is stimulated under a degree of anesthesia which will permit reflex retraction of the nictitating membrane and dilatation of the pupil, there is a primary increase of rate due to adrenal secretion, followed by the slowly developing increase characteristic of the thyroid effect. If the vagi and the cardiac fibers of the stellate are cut and the animal is asphyxiated under conditions which permit the eye changes described above, there is a similar primary rise due to adrenal secretion, followed by the secondary thyroid effect. If the thyroid glands have been previously removed, sensory stimulation and asphyxia induce only the increase of rate due to adrenal discharge.—I. B.

THYROID tumors of endothelial origin (*Tumori tiroidei di origine endoteliale*). Clivio (C.), *Pathologica* (Torino), 1922, 14, 759-772.

The author reports the cases of 2 patients with endothelial thyroid tumors with metastases, in one, in the lungs and stomach. and in the other, in the liver and bones. Such tumors are characteristically of long standing before any metastasis is formed. The histology of the primary tumors as well as of the metastases is reported in detail, showing that the growth was primary in the thyroid and that the tumors are true intravascular hemangio-endotheliomata.—G. V.

Basal metabolism of incipient tuberculosis. Its value in the prognosis of the tendency of development and in the detection of



**HYPERTHYROIDISM** fruste and aggravated (Métabolisme basal des tuberculeux incipients. Sa valeur dans le pronostic des poussées évolutives et le dépistage des hyperthyroïdies frustes et aggravantes). Cordier (V.), Compt. rend. Soc. de biol. (Par.), 1923, **88**, 782-784.

In incipient pulmonary tuberculosis (eliminating thermic influences) a sudden exaggeration of basal metabolism at the beginning of an evolutive "push" is a bad prognostic indication and, in the majority of cases, is correlated with a phase of hyperthyroidism that may be recognized by clinical signs and evidences of hyper-sympathicotonia.—T. C. B.

**Influence of irradiation of the THYROID upon the ADRENALS of the rabbit** (Influence de l'irradiation du corps thyroïde sur les surrénales du lapin). Coulaud (E.), Compt. rend. Soc. de biol. (Par.), 1922, **87**, 1072-1073.

Irradiation of the thyroid in doses sufficient to cause histological modifications determines a cortical hyperplasia of the suprarenals with increase in weight and volume.—T. C. B.

**Tryptophane, THYROID gland and tumor growth.** Cramer (W.), J. Physiol. (Lond.), 1923, **57**, lxi. (Proc.).

Rats fed on a vitamin rich diet, but in which the protein is supplied by maize (lacking in tryptophane), pass into a condition suggesting a lack of vitamine B. There is a characteristic atrophy of the thyroid. It is suggested that tryptophane is the mother substance of the thyroid hormone.—T. C. B.

**Surgery versus roentgen ray in the treatment of HYPERTHYROIDISM.** Crile (G. W.), J. Am. M. Ass. (Chicago), 1921, **77**, 1324-1326.

Comparing the results obtained by roentgen ray therapy reported in the literature and his own results with surgical treatment in hyperthyroidism, Crile feels that the evidence is definitely in favor of the latter method, particularly as the operative mortality under present conditions is practically nil. By surgical procedures much time is saved and a more certain cure is achieved.—W. M. A.

**HYPOTHYROIDISM and constitution** (Hypothyreoidismus und Konstitution). Curschmann (H.), Deutsche Ztschr. f. Nervenhe. (Leipz.), 1921, **68-69**, 40-55.

Myxedema-like syndromes have appeared frequently during and after the war, evidently as a consequence of the general under-nutrition, but there is also a certain relation to constitutional disposition. The thyroid appeared especially atrophic at autopsy of hunger edema subjects. It is possible that the atrophy of the thyroid in

under-nourished persons diminishes the metabolism corresponding to the conditions of nourishment. At the same time there is decline of temperature, bradycardia, lymphocystosis, etc. Myxedema sometimes appears at the time of the menopause. The author describes some diseases with signs of constitutional inferiority (not hypothyroidism proper) which caused myxedema, for instance, cardiovascular, secretory, psychical neuroses; angioneurotic edema; hemicraniosis; vertigo; familial hereditary syndromes with chlorosis; amenorrhea; congenital syphilis, coincident with syringomyelia and progressive muscular dystrophy.—A. B.

**Exophthalmic GOITER** and lesions of the adnexa uteri (*Goitre exophthalmique et lésions utéro-annexielles*). Delestre (M.), *Thèses de Par.*, 1920-21, 241.

According to Delestre, whose investigations have shown them to be present in 96%, lesions of the genital system are more frequent than is supposed in exophthalmic goiter. In young persons there is an ovarian insufficiency which is frequently congenital or familial. In older persons there is an ovarian insufficiency which is secondary to lesions of the uterus and adnexa. Genital disturbances usually precede the other symptoms of Graves' disease, and are not the result of the morbid syndrome. Delestre records a case of Graves' disease in which removal of a suppurating ovarian cyst caused considerable improvement of the general condition after hemithyroidectomy had produced no result.—*Med. Sc.*, 8, 287.

**Röntgen treatment of exophthalmic GOITER** (*Erfahrungen über die Röntgentherapie bei Morbus Basedowii*). Edling (L.), *Fortschr. a. d. Geb. d. Röntgenstrahlen* (Hamb.), 1923, 30, 117.

The value of x-ray treatment in exophthalmic goiter is very variously estimated and a large number of surgeons are opposed to it, while others admit its use. The author reports on 30 cases which came under his hands, in 25 of which the symptoms were very well marked. He regards the damage to the nutritive function as the essential characteristic, i. e., the emaciation and loss of strength as well as the not infrequent occurrence of glycosuria and the rise of temperature, the disorder of the vasomotor system, the rapid pulse, cardiac enlargement, diarrhea, and sweats. For him these are the symptoms of primary importance, and he is inclined to measure the results of the treatment by its effect upon them. He claims that of the 30 patients handled by the Röntgen method, in addition to the usual medical and hygienic treatment, 30% were relieved of all symptoms; 43.3% improved, and 20% either showed no improvement or died, while 6.7% suffered slight relapse. The great majority of the subjects were substantially improved within 4 months of the beginning of the treatment. The coincidence of the beginning

of convalescence with that of the treatment points to the latter as being the dominant cause of the improvement. The Röntgen treatment, compared with that by operation, yielded practically equally good results. The actual number of cures by operation is decidedly greater, and the cure is generally more complete than by the Röntgen method. The results are obtained more quickly, but surgical interference is associated with the danger of postoperative death from the disease, and this may occur not only in the very grave, but also in the less serious cases, and about 10% of those operated upon die. X-ray treatment fails in about 20% of the cases, and generally in those of the grave type. The causes of failure are not satisfactorily explained either by the general clinical characters of the case, by heart complications of any kind, or by social conditions, by a previously chronic course of the disease, or by variations in the radiation technique employed. They appear rather to be governed by, at present, unknown conditions which are probably to be attributed to insufficient pathological knowledge, and also to the rather vague demarcation of the disease. Measurement of disturbance of the nutrition gives us a far more certain means of diagnosis in the most characteristic types of the malady than any previously in use, and enables the results of the Röntgen treatment to be controlled with almost mathematical precision. At the same time it affords a means of obtaining information as to the progress of an individual case at any stage.—Med. Sc., 8, 435.

**The causes of surgical failure in HYPERTHYROIDISM.** Else (J. E.) & Irvine (H. S.), J. Am. M. Ass. (Chicago), 1922, 79, 1289-1291.

Else and Irvine believe surgical failure to be due to errors in diagnosis, overestimation of the patient's resistance, persistent symptoms due to delayed operation, recurrence of symptoms due to insufficient operation and improper after-care. They maintain that hyperthyroidism is a surgical disease and that operation must be performed early if permanent lesions are to be prevented. After-care is as important as the operation.—W. M. A.

**Exophthalmic GOITER** in a young woman with a familial history of diabetes mellitus. Fitz (R.), Med. Clin. N. Am. (Phila.), 1921, 5, 528-533.

The case reported is a girl of 20 whose brother and sister died of diabetes early in life. The patient was well until one month previously, when she probably developed an acute infection of unknown etiology. Her chief complaints were malaise, nervousness, and the loss of 5 pounds in weight. Urinalysis some time before had revealed a trace of sugar. Physical examination revealed septic tonsils; tachycardia, tremor, and a palpable thyroid gland presenting a thrill. Basal metabolism was +34%, leading to a diagnosis of

ing blood sugar concentration was within normal limits. Following exophthalmic goiter. Sugar tolerance was diminished, while the fast—an attack of acute tonsillitis while in the hospital the basal metabolism was +45%. The urine was sugar free. Tonsillectomy was performed without subsequent improvement in the patient's general condition. A few weeks later thyroidectomy was performed. Six weeks later the patient reported that she felt perfectly well. Fitz concludes that this patient, though apparently well, must be regarded as potentially diabetic and therefore should make use of the simple rules of diet.—I. B.

(THYROID) X-ray treatment in Graves' disease (Röntgenterapi ved morbus Basedowii). Fischer (J. F.), Ugesk. f. Læger (Copenhagen), 1922, 84, 346-362; 385-394.

Report of the x-ray treatment of 420 patients with Graves' disease. Cases of simple goiter were not included. "Formes frustes" was present in one-third of the subjects; one-third had slight cases and one-third had rather severe cases. Ordinarily no distinction can be made between thymic and thyroid forms of the disease. The results were less prominent in the subjects with a little goiter and there were insignificant nervous symptoms, but predominant tachycardia. As a whole the author obtained good results in four-fifths of the patients. In the other fifth there was no aggravation of symptoms except in one patient; however, in a similar case the subject died in the same manner without x-ray treatment. Most of the patients increased in weight. Hyperidrosis and diarrhea also disappeared rapidly. Tachycardia was cured in 25% and improved in 50% of the cases. As is the case after operation, exophthalmos was the most persistent symptom. The struma disappeared totally or partially in two-thirds of the patients and the remaining one-third were improved. In only a few patients treated in the private clinic did the goiter return. Recurrence was more often seen among the hospital patients, probably due to social circumstances (hard work soon after leaving the hospital). Fischer considers Krogh's method of basal metabolism determinations as good indication of the results of the treatment. Only in chronic cases and in those in which x-ray treatment is without effect is operation advocated.—K. H. K.

(THYROID) Flajani-Basedow's disease and undulant type of tuberculosis (Sindrome Flaiani-Basedow e febbre tubercolare a forma ondulante). Franco (P. M.), Folia med. (Napoli), 1923, 9, 361-370.

In this type of tuberculosis a thyroid manifestation is observed which disappears when the patient recovers from tuberculosis. In agreement with other authors, Franco thinks that the hyperthyroidism is of toxic origin or perhaps due to the action of toxins on the sympathetic system, having noted that there is a likeness in sympa-

thicotropic and autotrophic actions between tuberculosis poisons and thyroid secretion.—P. M. N.

**Studies on the relation of the THYROID to pancreatic DIABETES in dogs.** Friedman (G. A.) & Gottesman (J.), J. Am. M. Ass. (Chicago), 1922, 79, 1228-1233.

After summarizing the literature, Friedman and Gottesman report experimental work on a series of 50 dogs. Depancreatized glycosuric dogs became sugar free after complete ligation of the thyroid arteries or after thyroidectomy, provided tetany or infection does not occur, while partial ligation or unilateral lobectomy has no such effect. They suggest trying thyroidectomy in human subjects with diabetes which do not respond to modern treatment, notably in children.—W. M. A.

**Incidence of GOITER in college students (women).** Guilder (Ruth), Ann. Clin. Med. (Balt.), 1923, 1, 248-255.

Of 609 women students of the University of Illinois examined 276 (45.3%) had some degree of thyroid enlargement, the majority of these without any accompanying subjective or objective clinical findings referable to disordered thyroid function. Data from similar surveys of students in 6 other colleges or universities are referred to, and the statistical literature in general briefly reviewed.—E. C. A.

**THYROIDITIS.** Hallberg (C. A.), Ann. Clin. Med. (Balt.), 1923, 1 261.

Thyroiditis may be suppurative or tuberculous. Suppurative thyroiditis pursues the course of an acute localized infection leading to abscess limited to one lobe. Myxedema does not follow. The tuberculous thyroid is moderately enlarged and unusually hard, as it is in carcinoma. Clinical signs of tuberculosis may be lacking. The basal metabolic rate may be markedly elevated, leading to confusion with exophthalmic goiter. Onset may, unusually, be acute with local pain, tenderness and swelling, and with fever. Myxedema often develops. The diagnosis is manifestly difficult.—E. C. A.

**The effects of THYRO-PARATHYROIDECTOMY and PARATHYROIDECTOMY at 100 days of age on the growth of the reproductive system of male and female albino rats.** Hammett (F. S.), Am. J. Anat. (Phila.), 1923, 32, 37-51.

After both thyro-parathyroidectomy and parathyroidectomy the ovary and uterus not only stop growing, but actually lose weight. The effect is more marked in the "thypars." In the males, on the other hand, the growth of the testis and epididymis is but slightly retarded in the thyroidless animals and not at all in the "parathys." It is thus evident that the growth and probably the functional ac-

tivity of the sexually mature reproductive system of the female is greatly dependent upon the activity of the thyroid, while that of the male is relatively independent. The probability is strong that this inherent constitutional difference in sex gland thyroid relation is a factor in the greater incidence of thyroid disturbance, particularly goiter, in the female.—Abst., Wistar Inst.

The effect of **THYRO-PARATHYROIDECTOMY** and **PARATHYROIDECTOMY** at 100 days of age on the growth of the glands of internal secretion of male and female albino rats. Hammet (F. S.), *Am. J. Anat. (Phila.)*, 1923, 32, 53-74.

Thyro-parathyroidectomy accelerates the growth of the hypophysis in the male albino rat and retards that of the female. This sex difference is attributed to the modifying influence of the sex glands. Lack of thyroid secretion causes absolute inhibition of growth and devolution of the adrenals, pancreas, and thymus in both sexes. The thymus is the most sensitive. The lack of parathyroid secretion retards the growth of the hypophysis, adrenals, pancreas and thyroid of both sexes. Thymus involution is caused. The significance of these observations is discussed.—Abst., Wistar Inst.

Treatment of **GOITER** with small quantities of iodine (*Zur Frage der Kropfbehandlung mit minimalen Joddosen*). Haase (H.), *Wien. klin. Wchnschr.*, 1923, 36, 573.

In Austria there is now a severe goiter epidemic. The author recommends the use of small quantities of iodine. He uses an Austrian preparation, iodostrumit, containing 0.6 mg. NaI per tablet  
—J. K.

The precipitin reaction of **THYROGLOBULIN**. Hektoen (L.), Carlson (A. J.) & Schulhof (K.), *J. Am. M. Ass. (Chicago)*, 1923, 81, 86-88.

Rabbits were immunized by intravenous injections of dog thyroglobulin. Specific precipitating serum of high titre was obtained. Using this serum, the presence of thyroglobulin was shown in the lymph from the thyroid and cervical lymphatics of goitrous dogs but not in the thoracic duct lymph nor blood serum. The possible use of this method in physiological investigation of the thyroid and other glands is discussed.—W. M. A.

Pelvic findings in one hundred cases of toxic **GOITER**. Hertzler (A. E.), *Am. J. Surg. (Elmira, N. Y.)*, 1923, 37, 274-276.

Many patients who have thyroid enlargement and evidence of thyroid dysfunction present evidence also of disturbance of the pelvic organs either functional or anatomical or both. Among 100 cases, the following conditions were encountered: normality of

pelvic functions, 13; dysmenorrhea, 26; displacements, 7; dysmenorrhea with displacement, 10; metrorrhagia, 4; scanty flow, 4; myomas, 3; previous pelvic operations, 8; evidence of earlier chronic pyosalpinx, 7.—R. G. H.

**A clinical and pathological study of fifty cases of HYPERTHYROIDISM.** Hill (R. B.), Calif. State J. M. (San Fran.), 1923, 21, 163-165.

A brief review of the clinical and pathological differentiation of goiter. The author concludes that neither symptomatology nor pathology is constant. The symptomatology of a given case may change without a corresponding change in the histology of the thyroid. Hence a diagnosis made on clinical symptoms is more reliable than one in which the pathology of the thyroid is depended upon.

—I. B.

**Action of the THYROID dialysate.** Ihjima (K.), Tokoyo-Igakukai-Zasshi (Tokyo), 1923, 37, No. 4, 355-389.

A dialysate containing 0.001 mg. of iodine in 1 cc. was obtained from cows' thyroids by dialysis with parchment paper. Its actions upon the autonomic nervous system was observed in rabbits, rats, frogs and bull-frogs. The effects upon the vessels, the heart, the blood pressure, the pupil, the uterus and the intestine showed that the dialysate excites both the sympathetic and parasympathetic structures, although the symptoms were varied in different animals.

—S. K.

**Treatment of juvenile and parenchymatous GOITER with small doses of iodine** (Zur Behandlung des juvenilen und parenchymatosen Kropfes mit Jodminisimdosen). Kasper, Wien. klin. Wchnschr., 1923, 36, 473-474.

Splendid success is reported with the following preparation: 5 drops on the empty stomach of 4 mg. NaI, 25 cc. water.—J. K.

**An estimation of the pathogenesis and the evaluation of therapeutic procedures in exophthalmic GOITER.** Kessel (L.), Lieb (C. C.) & Hyman (H. T.), J. Am. M. Ass. (Chicago), 1922, 79, 1213-1215.

In order to establish a control for therapeutic measures the authors have allowed a series of 38 cases to run a "spontaneous" course. The patients were placed under conditions as ideal as possible in hospital wards for 6-10 weeks, after which they spent a month in the country. Two patients died, 1 of an acute crisis of the disease; and 2 had recrudescences. The course was controlled by basal metabolic rate determinations. There was a striking tendency for the rate to fall rather abruptly. On an average, 4 months after admission to the hospital the patients were restored to usefulness.—W. M. A.

**GOITER** in Telemarken (Strumaforekomsten i Telemarken). Kjölstad (S.), Norsk Mag. f. Lægevidensk. (Kristiania), 1921, 82, 729-739.

Kjölstad's survey of the Telemarken district in Norway shows that the incidence of goiter among school children in this district is extraordinarily high—higher, probably, than anywhere else in Norway. He diagnosed goiter only when the thyroid was visibly as well as palpably enlarged, and when in doubt as to the size of a thyroid being normal or enlarged he assumed it to be normal. Altogether 1,047 school children were examined, and goiter was found in 309 out of 537 girls, and in 285 out of 510 boys. By classifying the school children according to (1) the professional classes, (2) the farmer class, and (3) the laboring classes, he found that as the social scale descended the frequency of goiter ascended, the incidence of this condition being 33.3%, 55.7% and 61.3%, respectively, in the above classes. These figures referred to boys only; closely similar figures were obtained for girls. Kjölstad concludes that hygiene plays a certain part in the genesis of goiter, and he notes that investigations made by Schiötz in 1917 in another part of Norway showed the same differences when he classified the 10,000 school children examined according to their social and economic status.—Med. Sc., 8, 284.

The effect of the **THYROID** on the movements of stomach and intestines. Kobe (T.), Nihon-Naikagakukai-Zasshi (Tokyo), 1923, 11, No. 3, 233-280.

The movements of the stomach and intestines of men and rabbits were examined by means of x-rays. In normal men, a thyroid preparation caused an acceleration of these movements. The stomach of Basedownians was in the so-called sympatheticotonic condition and the rate of the movements of the contents was greater than in normal men. This relation was also found in the case of the rabbits. The weakened movements after thyroidectomy could be restored by a dose of thyroid preparation.—S. K.

**Relation between THYROID FUNCTION and alexin production.**  
Kobe (T.), Nihon-Naikagakukai-Zasshi (Tokyo), 1923, 11, No. 5, 468-496.

Normal rabbit's serum diluted to 1:20-40 has still the power to kill 5000 colon bacilli in 5 hours. The alexin content of the serum was increased by thyroid feeding, i. e., in this case a solution of 1:60 of the serum showed the same effect as the former. In almost all cases thyroidectomy had no influence upon the alexin production, although in some cases it was lowered for about 24 hours after the operation. These results are in accordance with those of Fassin. The alexin content of the thyroidectomized rabbits was slightly increased by thyroid feeding.—S. K.



(**THYROID**) The clinical application of basal metabolism determinations in man (*Sur l'application, en clinique, de la détermination des échanges gazeux d'homme*). Krogh (M.), *Compt. rend. Soc. de biol. (Par.)*, 1922, 87, 1222-1224.

An investigation of the metabolism in 3 types of patients (Graves' disease, other types of goiter, and obese patients), some of which were under treatment by thyroid. The determination of the basal metabolism, which may easily be carried out by the registering apparatus of A. Krogh, is of considerable value for the detection of slight cases of hyper- or hypo-thyroidism and for estimating the dosage and effects of treatment.—*Physiol. Abst.*, 8, 22.

Action of the **THYROID** extract upon bacteria. Kumatori (S.), *Chugai-Iji-Shimpo (Tokyo)*, 1923, No. 1041, 964-971.

Thyroid extract had no power to inhibit the multiplication of vibrio cholerae or bacillus coli communis. Typhoid bacilli cultivated in this medium, however, showed a decrease of their own agglutination value. This may be attributable to the action of some special substance contained in the thyroid which checks the agglutination. According to these facts, the hypothesis that the rareness of thyroid tuberculosis and the production of antibacterial immune bodies in the blood by thyroid feeding are both due to a colloidal substance contained in the thyroid hardly seems to be acceptable.—S. K.

The relation between the **THYROID** function and healing of the muscle wound. Kusakabe (S.), *Nihon-Naikagakukai-Zasshi (Tokyo)*, 1923, 11; No. 1, 17-40.

The author made a slight cut in muscle of rabbits fed with thyroid and of thyroidectomized rabbits. After a definite number of days the animals were killed and the muscles were examined histologically. The wounded muscles of the thyroidectomized rabbits sometimes showed intense degeneration and necrosis and the healing process was usually slow. The results were directly opposite on the rabbits fed with thyroid.—S. K.

(**THYROID**) Basal metabolism in the obese (*Le métabolisme basal chez les obèses*). Labbé (M.) & Stévenin (H.), *Compt. rend. Soc. de biol. (Par.)*, 1923, 88, 9-12.

In a study of 46 subjects the basal metabolism was normal in 27, in 13 subnormal, and above the normal in 6. In those with subnormal basal metabolism thyroid treatment gives excellent results; in the subjects with normal or hypernormal metabolism no benefit is obtained, and its administration may even be dangerous.

—*Physiol. Abst.*, 8, 22.

Prevention of **GOITRE**. Marine (D.), *Pub. Health, Mich. St. Bd. Health*, 1923, 11, 23-24.

Simple goiter is the easiest known disease to prevent; 100-200 mg. of iodine taken twice a year is sufficient to prevent the disease. The maximum storage capacity of thyroid gland is not over 30 mg. —Physiol. Abst., 8, 185.

Pathological-histological alterations in the circulatory organs and in the kidney after administration of **THYROID** preparation. Matsuka (K.), Nihon-Naikagakuakai-Zasshi (Tokyo), 1923, 11, 299-344.

Observations were made on rabbits, dogs and goats. Arteriosclerosis was found in the aorta after administration of thyroid preparation, and it was more intense if a preparation of gonads corresponding to the sex of the animal was added. The author thought that such arteriosclerosis was not caused by the iodine of thyroid extract, but by an unknown substance contained in it, for iodine has a preventative action upon arteriosclerosis. In the heart he found both general degeneration and local necrosis of the heart muscle. The former seemed to be caused by some toxic substance from the thyroid extract, and the latter by arteriosclerosis of the vessels of the heart wall. In the kidney a slight parenchymatous degeneration was found, but it is difficult to say with certainty if it was caused by a toxic substance of the thyroid or by the fact that a herbivorous animal such as a rabbit was fed with a thyroid preparation which contains protein.—S. K.

Histological changes in the peripheral nerves caused by the disturbed function of the **THYROID**. Matura (A.), Nihon-Naikagakuakai-Zasshi (Tokyo), 1923, 11, No. 1, 1-16.

The author found so-called segmental degeneration in rabbits fed with thyroid, and swelling, vacuolization, and liquefaction of the axis cylinder in those with thyroidectomy. The author believes that the former is due to intoxication by thyroid substance, and that the latter is a result of a nutritional disturbance of nerve fibres caused by the elimination of a hormone. The changes caused by thyroidectomy could not be restored by administration of the thyroid preparation; moreover, this caused an intoxication phenomenon.—S. K.

Blood sugar and basal metabolism: Findings in chronic pulmonary tuberculosis and **HYPERTHYROIDISM**. McBrayer (R. A.), J. Am. M. Ass. (Chicago), 1921, 77, 861-863.

Studying 44 cases of chronic pulmonary tuberculosis as regards basal metabolic rate and blood sugar level, McBrayer concludes that in about one-third of the cases both of these are increased; in about one-fifth one or the other is increased; and very seldom does one find both decreased or one decreased and the other normal. Therefore, these examinations are of no value in differentiating chronic pulmonary tuberculosis and hyperthyroidism.—W. M. A.

**Discussion on exophthalmic GOITRE.** Murray (G. M.), Brit. M. J. (Lond.), 1922, ii, 908-910.

Murray states that in 300 cases of exophthalmic goitre seen in private practice between 1911 and 1921, the disease occurred 3 times as often in women as in men. In another series of 120 cases reported by him in 1903 the proportion was exactly 11 to 1. Sex is therefore still one important predisposing factor. In no less than 77%, no other predisposing or exciting cause was found. A family history was obtained in nearly 9%. A sudden nervous strain had occurred in 13%, while prolonged periods of anxiety or worry were recorded in 6%. Overwork was given as a cause in 4%, and nursing, chiefly in war hospitals, in 3%. Exophthalmic goitre does not often follow physical injuries, as in only 3% had an accident occurred, and 2% had recently undergone an operation. None of the cases had followed a war wound, and in another series of 15 soldiers under Murray's care, suffering from hyperthyroidism, none had been wounded.—Med. Sc., 8, 285.

**The iron content of the blood in THYROIDECTOMIZED animals**  
(Sul contenuto in ferro del sangue negli animali stiroidati).  
Parhon (Marie), Endocrin. e. patol. costit. (Rome), 1922, 1, 39.

In 6 weeks old sheep, after removal of the thyroid, the iron content of fresh blood fell to 0.053% from a normal figure of 0.065%, of dried blood to 0.273% from 0.328%. A relation is suggested between this and the lowered oxidations of the body.

—Physiol. Abst., 8, 184.

**(THYROID)** A case of trophedema (Un caso de trofoedema).  
Pereire (A.), Siglo méd. (Madrid), 1923, 71, 721.

Pereire describes a case of trophedema in a girl 16 years of age with irregular cretinoid aspect and with marked mental deficiency. One to 10 gm. desiccated thyroid daily caused notable improvement. The author agrees with Hertoghe and Bacon that thyroid insufficiency plays a rôle in trophedema.—E. B.

**The treatment of HYPERTHYROIDISM by radiation.** Pfahler (G. E.), Med. Clin. N. Am. (Phila.), 1921, 5, 853-865.

In the diagnosis of hyperthyroidism the basal metabolism test is of value, but the preliminary starvation, the expense, and the required expertness in its performance interferes with its general adoption as a diagnostic measure. The Bram quinine test is devoid of objections, seems to have considerable value, and has given Pfahler satisfactory results. The Goetsch test involves some risk and seems to make some patients distinctly worse. Tachycardia is of diagnostic value, while exophthalmos is inconstant. Surgery is associated with considerable risk and frequently results in recurrence or in

**Hypernephrosis.** Bearing in mind the associated risks, nephrectomy is to be resorted to when symptoms and circumstances demand such results. Endemicity on the other hand does not ordinarily require intervention, and results through degeneration would in most cases be symptomatic and satisfying. Intervention following such occurrence of hypernephrosis depends on the following order: 1. Increase in weight due to increase in weight and improvement in various symptoms and in function. The chronic enlargement and atrophy of the kidney are among the last symptoms to disappear. In Phyllis's experience these results are usually permanent. Endemic may be associated with greater symptoms than acute. Since it can be treated without the patient's knowledge of the nature of the symptoms it is particularly useful in those cases in which because of existing or apprehended other means of treatment are inadvisable.—L. E.

**The use of work in HYPERNEPHROSIS.** Phyllis E. S. & Smith T. J. Am. J. Physiol. Path. 1931. 22: 107-117. 1931.

In this study there is evidence of a correlation between the degree of renal and metabolic control and there is a marked lower value in many values for the same amount of control work. The experimental feeding metabolism induced by dietary control is related to the work—Physiol. Abs. 8: 1-1.

**General features of HYPERNEPHROSIS.** Phyllis E. S. & Smith T. J. Am. J. Physiol. Path. 1931. 22: 107-117.

Distention of the kidney is observed in nephrectomy with a basal metabolic rate of —10. Such a patient gives typical hypernephrosis signs: a rise in basal metabolism from 11 hours after reaching its height in about 11 days and lasting sometimes for 10 weeks. Symptoms of hypernephrosis proper are associated with an increased metabolic rate which is probably due to an increase in thyroid and possibly a peritonitis of it. Increased increases in metabolic rate are possibly associated with adrenal activity as the evidence is seen. The accompanying symptoms although consistent and probably due to thyroid hyperactivity are quite similar to those accompanying the more prolonged case of hypernephrosis proper. In the narrowest very slight case is sufficient to bring on these symptoms and may lead to confusion or depression. Depression should be based on repeated examinations together with several for secondary effects of a prolonged increase in metabolism or loss of weight persistently been but not in mild and various degrees of the functional muscle.—L. E.

**Relative value of surgery and treatment in the treatment of HYPERNEPHROSIS.** Phyllis E. S. & Smith T. J. Am. J. Physiol. Path. 1931. 22: 107-117.

After reviewing the results of roentgen ray therapy in 58 cases of hyperthyroidism reported by Means and Holmes, and similarly the results in 30 cases in which surgical treatment has been completed, Richardson concludes as follows: (1) subtotal thyroidectomy is a more effective form of treatment of exophthalmic goiter than roentgen ray treatment; (2) the roentgen ray has a beneficial result in certain cases of hyperthyroidism; (3) if after 4 months of roentgen ray treatment the degree of improvement does not promise "cure," operation should be undertaken.—W. M. A.

**THYROID treatment of Dercum's disease** (*Zur Schilddrüsenbehandlung der Dercumschen Krankheit*). Reichmann (F.), *Deutsche med. Wchnschr. (Berl.)*, 1923, **49**, 1018-1019.

In this case thyroid treatment had a good effect, but in most cases described in the literature thyroid medication has had no influence.—J. K.

**Effects of castration on the THYROID** (*Gli effetti della castrazione sulla tiroide*). Scala (G.), *Folia med. (Napoli)*, 1921, **7**, 423-430.

There is first hypersecretion, but later the secretion diminishes and causes augmentation of the connective tissue.—P. M. N.

**The influence of the THYROID on the creatine-creatinine metabolism** (*Der Einfluss der Schilddrüse auf den Kreatin-Kreatinin-Stoffwechsel*). Schenk (P.), *Arch. f. exper. Path. u. Pharmakol. (Leipz.)*, 1922, **95**, 45-63.

In rabbits the creatinine varies between 3.125 and 4.230 mg. in 100 cc. blood. Thyroidectomy does not influence the blood creatine in a regular manner, but brings the rate near the lower normal limit. The excretion of preformed creatine varies between 45 and 54 mg. per kg. body weight within 24 hours. It decreases after thyroidectomy and remains lower than in normal animals. During hunger it does not increase as is the case in normal animals. Feeding of thyroid extract causes a distinct increase of creatinin excretion in thyroidectomized animals.—A. B.

**Notes on the intestinal theory of exophthalmic GOITRE.** Slesinger (E. G.), *Practitioner (Lond.)*, 1923, **111**, 266-272.

Adrenin and thyroxin are said to be derived from tyrosin and tryptophane, respectively. These substances are the result of bacterial action on the proteins in the intestine. An excess production gives the thyroid and adrenals an opportunity for over-secretion. It is suggested that if this is the case, intestinal conditions may have a direct bearing on the disease.—J. C. D.

**Hyperglycemia in animals with THYROID disorders** (*Hiperglucemia adrenalínica en animales tiroideos tomizados*). Sopeña & Negrin, Arch. de med. cirug. y espec. (Madrid), 1923, 10, 74-80.

Experiments were performed on dogs and rabbits. In 3 normal dogs the injection of 1.0 mg. of adrenalin produced an increase of hyperglycemia of 25-82%. In dogs which had recently undergone thyroidectomy there was an increase, although not so marked as in the normal dogs. In those injected some time after thyroidectomy the increase was similar to that in the normal animals.—E. B.

**The desperate risk GOITER.** Tinker (M. B.), J. Am. M. Ass., (Chicago), 1922, 79, 1291-1294.

This report is based on 1000 selected cases under observation for 7 years. Tinker discusses what he means by a desperate risk case, paying particular attention to pulse rate, myocardial insufficiency, blood pressure, gastro-intestinal symptoms and basal metabolic rate. Pre-operative and post-operative care is outlined and emphasized. No figures are given as to results.—W. M. A.

**(THYROID)** A case of myxedema with pluriglandular disturbances (*Sopra un caso di mixedema con distrofia pluriglandolari*). Trenti (E.), Policlin. (Roma), 1922, 29, 307-318.

Trenti records a case in a man, aged 33, who, without any known cause, developed symptoms of myxedema associated with signs of suprarenal and pituitary insufficiency. Considerable improvement took place under thyroid treatment.—Med. Sc., 8, 296.

**The effect of heat upon operations for exophthalmic goiter.** Walton (A. J.), Brit. M. J. (Lond.), 1923, i, 1043.

In the last few years the operative results in cases of exophthalmic goitre have enormously improved, and although the average mortality remains somewhere in the region of 5%, statistics of individual operators have reduced this figure. In the last series published by Pemberton there was a mortality of only 1% in 1,093 cases. In spite of this, death will occasionally occur when least expected, and all are agreed that there is some factor at present not fully understood. The dangers of operation can be classified under three headings: (1) those directly resulting from the disease and the effects of the disease; (2) those directly due to accidents such as hemorrhage, pulmonary embolism, etc.; (3) those the joint result of disease and accident. However, care in the technique has done much to lessen the danger of groups (2) and (3), so that they are now no longer specially applicable to this disease. In the first group danger still remains from the fact that many of these patients do not seek operative treatment until there are secondary heart changes. The other great danger is the presence of hyperthyroidism, and although

this can be much lessened by careful attention to preliminary treatment, technique of operation, and to the anesthetic, the extent of hyperthyroidism following operation is still found to be variable. Two distinct groups of cases can be recognized. The one, best described as the vascular group, occurs in young females with a large, soft thyroid, marked exophthalmos, and a rapid pulse; the second, best designated as the nervous group, is seen in more elderly patients with a smaller and more nodular thyroid and more marked nervous symptoms. As a general rule the first group shows less postoperative reaction. The author has been struck by the fact that all cases of hyperthyroidism stand heat badly, and in spite of precautions to overcome the effects of heat it had seemed that the mortality during very hot weather was abnormally high. In the present communication he analyzes the results of his operations in the different months of the year, and a curve is plotted showing these results. It was found that in the months of February, March, April, May, September, October and November there was no mortality at all, but in the three months of June, July and August the mortality had risen to 20%. The figures upon which this curve was based were collected over a period of 10 years, so that this was probably not an accidental finding. Stress is laid upon the fact that in the extremely hot periods the case should be watched and operation delayed until cooler weather sets in.—Med. Sc., 9, 44.

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# Endocrinology

*The Bulletin of the  
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## Internal Secretions

March, 1924

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### STUDIES ON DIABETES

KARL PETREN\*

LUND, SWEDEN

Among those patients not previously treated in the hospital but who died there in coma, the duration of the disease, in my experience, has never been over four years, which shows the importance of the duration of the disease in prognosis. Taking those patients into consideration who were treated at the clinic and who later succumbed at home, we found several cases of more than four years duration, thus confirming the conclusion that treatment had a favorable influence on the duration of the disease.

I have found the blood sugar ratio at coma to be about 0.5-0.6 per cent or somewhat higher, but not below 0.45. The blood sugar in diabetes in which death results from an acute infectious disease (such as suppurative peritonitis, gangrene of the lower extremities, pyelitis, pneumonic diseases) may, however, be just as high (0.45-0.60 per cent). In a case of appendicitis an opportunity was obtained three days before death to determine the blood sugar ratio (0.115 per cent). The highest

\*A summary prepared at the request of the Editor. Prof. Petren's extensive studies are now available in book form, as announced elsewhere in this issue.—Ed.



blood sugar that I have found in which coma has not immediately set in has been 0.42 per cent. Undue increase of the blood sugar (i. e., 0.3 per cent) leading to coma need not come sooner than one or two days before death.

Even in severe diabetes, the N-metabolism is not higher than in health; I have even seen a few subjects in whom the ratio of changed albumen (gm.) to the body weight (kg.) has been below the lowest value so far noted in a healthy subject (i. e., Siwen 0.22). The fact that the N-metabolism is not increased in diabetes is likewise true in case of coma. Coma is not associated with destruction of protein unless complicated by an acute infectious disease; the same is true in cases of severe diabetes without coma, whereas even the slightest infections are able to produce a pronounced destruction of protein and greatly increased metabolic disorders.

Labbé's idea of denitrification as a regularly occurring phenomenon in severe diabetes is thus confuted, as is Chabanier's conception of a certain threshold for the blood sugar below which acidosis necessarily sets in.

The necessary condition for reaching the lowest N-metabolism (often 2-3 gm.) in diabetics as well as in healthy persons consists in a sufficient caloric intake. However, I have been able to attain a very low N-metabolism at a lower caloric intake than has hitherto been obtained in experiments on healthy persons. In these experiments carbohydrate was given only in small quantities, sometimes only 30-50 gm., but usually a little more than 50 gm. No investigator has previously observed that a really low N-metabolism can be reached without a large carbohydrate intake. The fat intake has naturally been abundant in all the cases in question.

It has been stated that even in case the N-metabolism before the fasting day has been at 3 or 4 or even below 3 gm., one or two fasting days will still be able to reduce the amount of the changed N considerably. The observations prove that to get such a diminution of the blood sugar it is necessary that a certain surplus of nourishment be supplied the days before the fasting days (so that there will be available nourishment "in the first-summons to arms" during the fasting days). Even a diet over several days consisting of butter only (sometimes also with cod-liver oil) exercises the same influence on the N-metabolism.

I believe, after my experience, that a fat intake up to 300 gm. does not have an unfavorable influence upon acidosis, but that the deciding factor in the acidosis of severe diabetes is the quantity of N-metabolism.

It has been concluded from these results that in every case of severe diabetes there is a threshold for the N-metabolism, above which acidosis ensues. If, however, the N-metabolism is brought below this threshold, the acidosis diminishes and disappears from whatever height it may have reached. This threshold may sometimes be as low as 3 gm. or even lower, i. e., so low that the maintenance of life may finally be rendered impossible.

Fasting days as a rule diminish acidosis, and I have been able to prove that this occurs through the lowering of the N-metabolism, which in its turn diminishes the acidosis. The same explanation holds for "pure fat days," although an increase of acidosis may sometimes occur.

Carbohydrate withdrawal in diabetes as well as in health causes moderate acidosis, but the marked acidosis ending in coma and present only in severe diabetes results from the extreme sensitivity of the N-metabolism which is a pronounced characteristic of severe diabetes; this sensitivity appears in the severest cases of diabetes even if the N-metabolism is very low.

In more than half the cases observed during recent years the blood sugar returned to normal. The material comprises only those cases in which the blood sugar once reached at least 0.24 per cent, which, according to my experience, means a form of disease in which coma is the expected termination—unless very strict diet restrictions permanently continued by these patients overthrows our present experiences regarding the prognostic value of such blood sugar amounts. Such reduction of blood sugar must then be attributed to the greatly reduced N-metabolism, because the carbohydrate intake in the form of vegetables is always given in free quantities, and because the fat intake is large—as a rule more than 200 gm.

According to my researches, a meal free from carbohydrates and relatively rich in N raises the blood sugar curve about 0.015%. It is not uncommon in diabetes for the blood sugar curve to be lower in the afternoon than in the morning before breakfast. Even in severely affected diabetics who have been

subject to stringent dietetic restrictions the blood sugar curve may remain uninfluenced by meals; this has been observed after administration of carbohydrates up to 38 gm. The degree of mobility of the blood sugar curve (in other cases of diabetes) does not have any regular relation to the temporary height of the blood sugar curve.

In diabetes there is a considerable curve fall on fasting days during the first six hours of the day; a slight fall takes place during the following six hours, but during the last twelve hours (at night) there is no regular fall. Even in health the blood sugar curve regularly falls during the first fasting day, with a ratio ranging between 0.01 and 0.03 per cent—contrary to that which has hitherto been looked upon as an axiom, viz., that it ought not to vary. On the other hand, the curve seems to be unaffected the second fasting day.

Fasting days and pure fat days reduce almost entirely and without exception the hyperglycemia in diabetes. The first of either of these sorts of days brings, on the average (calculated from a fairly large number of observations), a reduction of the blood sugar of 0.027-0.029 per cent and for two continuous days of either fasting or pure fat a reduction of 0.042-0.045. If the fasting days are repeated later on their effect on the blood sugar curve seems to diminish, which cannot be the consequence solely of the now present degree of hyperglycemia. As a matter of fact, the blood sugar reduction is the same for fasting days as for pure fat days, which proves that fat in the amount used (not more than 200 gm.) does not influence the blood sugar curve.

By blood sugar estimations on an empty stomach I determined the blood sugar threshold, past which glycosuria sets in. In my experience the conception of a gradual increase of this threshold during the course of the disease is inaccurate; the younger the patient, especially under 20 years of age, the higher the threshold with a higher quotient. If the threshold in question decreases during treatment this should, in a certain measure, have a prognostically unfavorable significance.

Hypertension without any clear signs of nephritis never produced hyperglycemia. Even in case of chronic interstitial nephritis the blood sugar is usually normal. There are a few deviations from the last rule, it is true, but it almost always

seems to be a question of prelethal conditions. (These conclusions are partly founded on an analysis of the literature.)

In a great number of the published cases (53 in number) there was no carbohydrate tolerance when the subjects were admitted, and consequently the D:N quotient could be calculated; in all except one of these patients carbohydrate tolerance was reached during treatment; sometimes even more than 150 gm. could be tolerated. Since the attainment of some tolerance for carbohydrate in such subjects cannot be due alone to a reduction of carbohydrate intake, and since the N-intake has likewise been much reduced, one must come to the conclusion that the quantity of the N-metabolism in these severe cases of diabetes has a great deal of influence on the variations of the tolerance for carbohydrate.

This delicate sensitivity to the N-metabolism is observed both in a study of the acidosis and of the blood sugar curve as well as in an investigation of the variations of carbohydrate tolerance.

After systematic treatment (in addition to the dietetic restriction opium has also been used regularly) a subjectively good state of health has been attained and in the majority of patients there has been an increase of weight when the course of the disease has not been unsatisfactory. In this connection the coma cases have not been taken into consideration, which issue of the disease I have seen in no small number. The majority of subjects in coma succumbed during the first three days of treatment; only a very few patients succumbed during the second week; while after thirteen days of treatment there has not been a single case of coma in the clinic for at least seven years. In four out of about a hundred cases of diabetes the cause of the unsatisfactory result was that the subjects had taken too little food, which compelled me to recommend an increased diet. These four cases are, however, examples of a limitation of the effect of this treatment which is found in the very nature of the disease itself. In only one case does the lack of improvement remain unexplained.

I have compared the effects obtained by my dietetic method and those obtained by Joslin, whose method is only slightly different from that of Allen. My results seem to have been better from a symptomatic point of view. Allen's material,

however, is not published in such form as to be easily compared.

Odin has reported a new modification of Van Slyke's method for determining the carbonic acid capacity of the blood which shows technical progress, and I have published a few results obtained by his method. As yet, however, this is to be looked upon as only a preliminary communication.

Among the fatal cases of diabetes which have been observed in the clinic or which have been seen in later examinations (altogether 89 in number) the frequency before 30 years of age is practically the same in the two sexes, but after that age the disease predominates in the male. I have concluded, therefore, that the disease before 30 years of age is due to endogenous causes, in all probability always hereditary, but that in the fourth decade exogenous factors might gain sufficient importance as to cause at times also fatal diabetes.

My researches regarding the amount of bilirubin in the blood in diabetes have demonstrated that when the blood sugar is normal bilirubin is, as a general rule, also normal, while there is often an increase of bilirubin in hyperglycemia. A further series of determinations in the same patients show that the curve of bilirubin may parallel the fall of the blood sugar curve during treatment; this proves that there is a certain relation, if not quite constant, between the quantity of blood sugar and bilirubin in the blood. Consequently the former theory is refuted that the analysis of bilirubin permits a classification of diabetic cases into those with or without an affection of the liver.

A series of cases are reported in which the D:N quotient was very high for many days, denoting, perhaps, the formation of sugar from fat. I do not believe, however, that any positive decision can be drawn from these cases.

Analysis shows that in a large number of subjects an increase of thecretory function of the pancreas set in during the dietitic treatment.

The fecal analyses made by Malmros, which are reported in the book, show that the quantity of N in the feces during severe N-restrictions in the food is between 0.5 and 1.0 gm. The variations within those limits are probably due to constitutional factors in the different individuals. In the feces of fasting subjects the N decreases to 0.20-25 gm. There are no earlier researches along this line except those of Friedrich Müller in

1889. His estimations are as low as 0.1-0.2 gm., and later of Benedict (not lower values). This endogenous N in the feces of fasting patients ought probably to be added to the N in the urine in order to estimate the true value of the N-metabolism.

Malmros' determinations show that the resorption in my dietetic method is satisfactory. The calculated losses for fat amount only to 1.4-6.3 per cent; for carbohydrate, 10-12 per cent (in the diet carbohydrates are given only in the form of vegetables, especially green vegetables).

An estimate of the probable average fault in duplicate analyses of blood sugar (calculated from 285 analyses) gives a value of only 0.001 per cent or about 1 per cent of the normal amount of blood sugar.

# CLINICAL EXPERIENCES IN ORGANOOTHERAPY WITH SPECIAL REFERENCE TO THE STIMU- LATION OF BODY GROWTH

THEODORE A. MCGRAW, JR., M. D.

DETROIT

There is probably no recent method of therapy that has aroused such acrimonious dispute as that of organotherapy, the use of animal glandular extracts to supplement those produced in the body in cases where the activity of the gland is thought deficient.

The literature of the day is crowded with articles written by misguided enthusiasts who, having mistaken nebulous theory for scientific fact, argue from false premises toward absurd deductions. As a result both of such writings and of the propaganda of certain of the commercial houses, we see an ever increasing army of practitioners who are prescribing shot-gun mixtures of glandular extracts, usually and fortunately in too small doses to cause much harm. Such a situation is throwing the whole science of endocrinology into ridicule and disrepute. It is not surprising that at a meeting of the Congress of Internal Medicine a man of national reputation whose special interest is the thyroid was heard to exclaim, "Endocrinology? No, call it Mythology!"

But as usual there are two sides to the matter. So, on the other hand, we have those ultra-scientists who demand that everything new must bear the hall-mark of laboratory proof before it can be accepted at all, forgetting that some of our greatest therapeutic advances have been accomplished without laboratory or experimental aid. Many of these critics have practiced organotherapy, but in a very half-hearted manner over much too limited time, *expecting* and getting very poor results.

Between these two classes there is room and need, I think, for thoughtful students of ductless gland diseases who, though not carried away by unwarranted enthusiasm, are willing to

devote careful study to the clinical aspects of the subject, using laboratory help whenever possible, yet not disregarding well-proved clinical results in the absence of laboratory confirmation. While not deerying the help of the laboratory, for discoveries such as thyroxin and the basal metabolism estimation marked a great advance in endocrinology, let us not overlook the tremendous asset of the *clinical* experiences of observers all over the world.

It is the intention of the writer to present in this article a number of clinical experiences with organotherapy, the patient in every case being a child suffering from retarded physical development. As will be seen, while some patients showed very



definite symptoms of glandular dystrophy, others presented no signs, or very slight ones, of endocrine disturbance. Therefore, for the purposes of this article the patients easily fall into the very simple classification given below. However, only such patients as have been treated for a reasonable time, usually a year or more, will be reported so that some types deserving mention will necessarily be omitted.

Patients classified as follows: Retarded physical development.

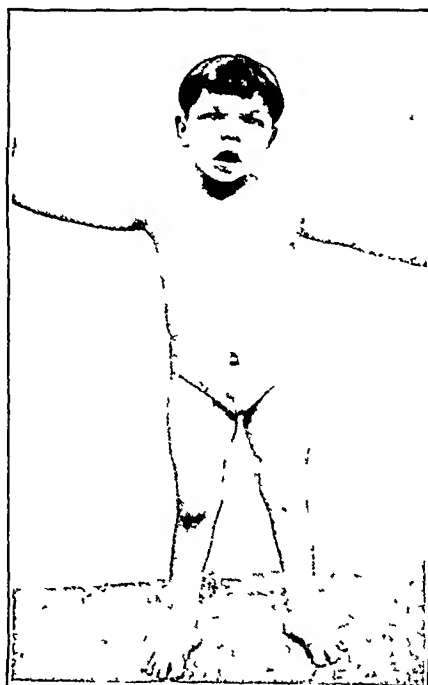
1. With definite symptoms of endocrine disease.



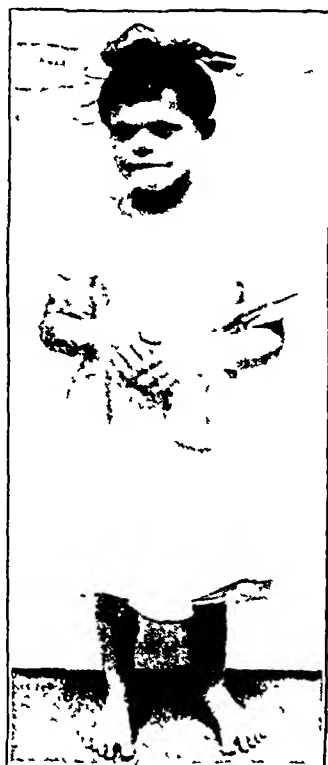
## 2. Without definite symptoms of endocrine disease.

Many of the cases showed delayed mental development as well, and a future article will record the effect of endocrine treatment upon their mental retardation.

As it is beyond the scope of this paper to take up etiology, symptomatology or pathology of the various types of endocrine disease except as they have a bearing upon the treatment or



CASE I, AGE 10  
AFTER THYROID TREATMENT



CASE I, AGE 11, AFTER  
PITUITARY TREATMENT

the results of treatment, the case histories are presented without further preamble.

Fourteen cases are presented, the first nine belonging to Group 1, the balance to Group 2. The first four cases are cretins.

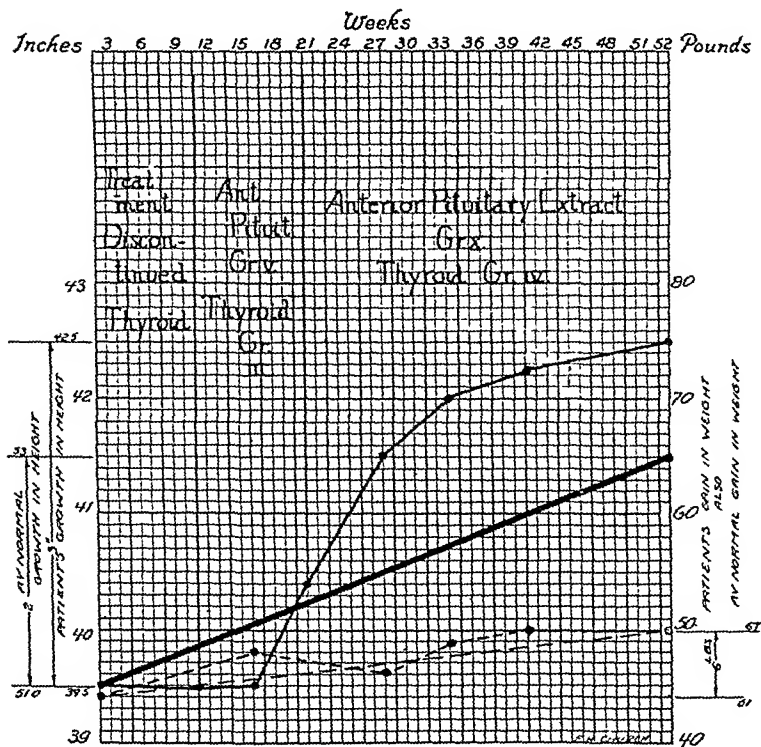
#### CASE I. CHILDHOOD MYXEDEMA

*Case I.* J. B., an inmate of the Michigan Home and Training School. Admitted when 7 years old, she was then the size of a child of 3. (See illustration.) As is often the case with these public charges, there was no one from whom a history could be obtained. She showed, however, all the signs of childhood myxedema, including

the large protruding tongue, open fontanelles, no teeth, coarse hair and a harsh, dry skin. She could not talk or stand alone. For 3 years, or until she was 10 years old, she was given thyroid extract—although at times intermittently—and that miraculous improvement took place which so often obtains in such cases. The fontanelles closed, the teeth erupted, the size of the tongue diminished and the skin became soft. Yet there was only a very slow mental and physical growth.

JUSTINE B. CASE I CRETIN

### Height and Weight Chart for 52 Weeks



Date Started JUNE 8, 1920

MENTAL RETARDATION ABOUT 8 YEARS

Age 10 YRS

PHYSICAL RETARDATION ABOUT 3 1/2 YEARS

At this time she came under the writer's observation. During the 3 years on thyroid alone she grew 10½ inches, but the most rapid growth took place during the first part of that period. During the 9 weeks she was under observation without treatment she did not grow at all. Chart 1 shows what took place in this case, and an explanation of these charts is now necessary.

This chart is designed to represent graphically the changes in height and weight of a patient under treatment in comparison with the average development in height and weight of a normal child of the same age. The chart covers 1 year divided into 3-week periods, three weeks being the average time between examinations. The extract prescribed, with the duration of its administration, is recorded on the upper part of the chart. On the left side is the scale representing the height in inches and one-tenth inches, while the weight in pounds is on the right side. The solid straight line running from left to right represents the average growth of the normal child of the same age as the patient, while the solid irregular line shows the growth of the patient during the year. The dots on this line signify the dates of examination with or without changes in prescription. Likewise, the straight broken line shows the average normal gain in pounds, the irregular broken line the patient's gain or loss in weight. By means of this chart then, it is possible to represent the kind and duration of treatment and the results obtained therefrom in terms of the height and weight of the patient and also to compare the patient's growth and development with that of the average normal child of the same age.

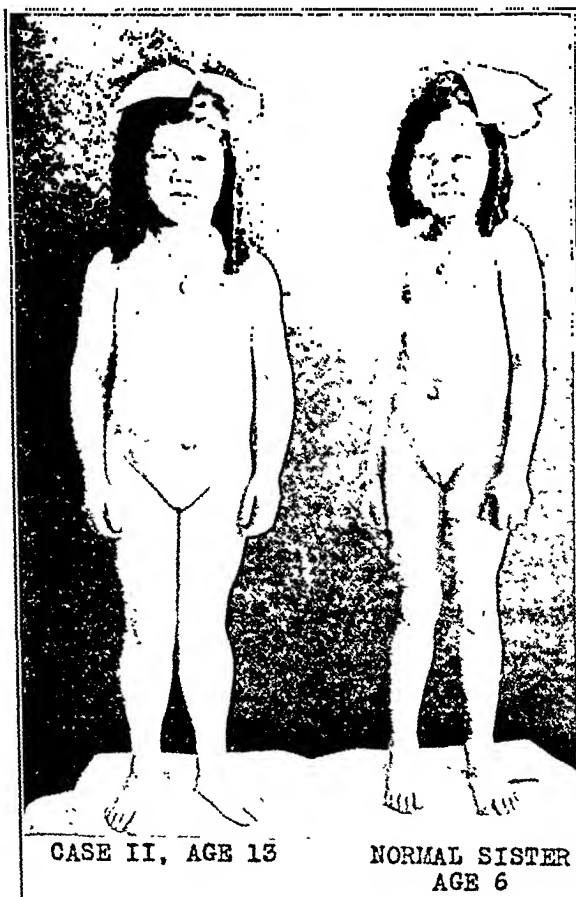
#### Illustration by use of chart of Case 1.

The patient was 10 years old. Normal height for that age averages 51 inches and rate of growth is 2 inches per year. The solid black line running from the lower left edge upward and to the right with an elevation of 2 inches on the scale represents this normal rate of growth. But the patient was only 39.5 inches in height when she came under observation, and the irregular solid dotted line shows her progress. For nine weeks she received no treatment, and at the end of that time examination showed that no growth had taken place. Now it has been fairly well determined both by animal experimentation and by clinical observation that the anterior lobe of the pituitary plays an important part in the growth and development of the body, exerting an influence in an even greater degree than the thyroid. So treatment was started by adding 5 grains of the anterior lobe pituitary extract daily to the daily dose of 3 grains of thyroid extract which she was accustomed to take. She took this prescription for 10 weeks; at the end of the first five she showed no growth, but during the second five weeks she made a remarkable growth of nine-tenths inch. The medication was now increased to 10 grains of anterior lobe and 4 grains of thyroid daily. Seven weeks later she had grown 1.1 inches more, greatly exceeding the normal rate of growth, as may be seen by comparing the two lines. In 1 year and 10 months under this treatment she grew 4.75 inches, or at the rate of  $2\frac{1}{2}$  inches a year, a rate for her age a little above normal. However, more important than the growth was the striking improvement in intelligence and locomotion. She made such marked mental improvement that she was transferred to a higher grade colony; she can now talk a little and shows a lively interest in her surroundings. Before treatment she could not stand alone; now she can walk fairly well. So it may be fair to say that this patient made notable improvement under thyroid plus anterior pituitary feeding, improvement that did not manifest itself under thyroid extract alone.

## CASE II. A. V. CRETIN

*Family History* is bad. The father and one grandfather were alcoholic. The mother had a positive Wassermann. The father's sister had myxedema.

*Personal History:* She was born after a normal pregnancy at full term. She walked late, but talked at the usual time. She was always in good health, but retarded mentally and physically. When 7 years old her Wassermann was 4 plus. The first record of her development, at 7 years, showed 40.5 inches height and 52 pounds weight. A normal height for a child of 4½ years, and 5 pounds overweight for her height.



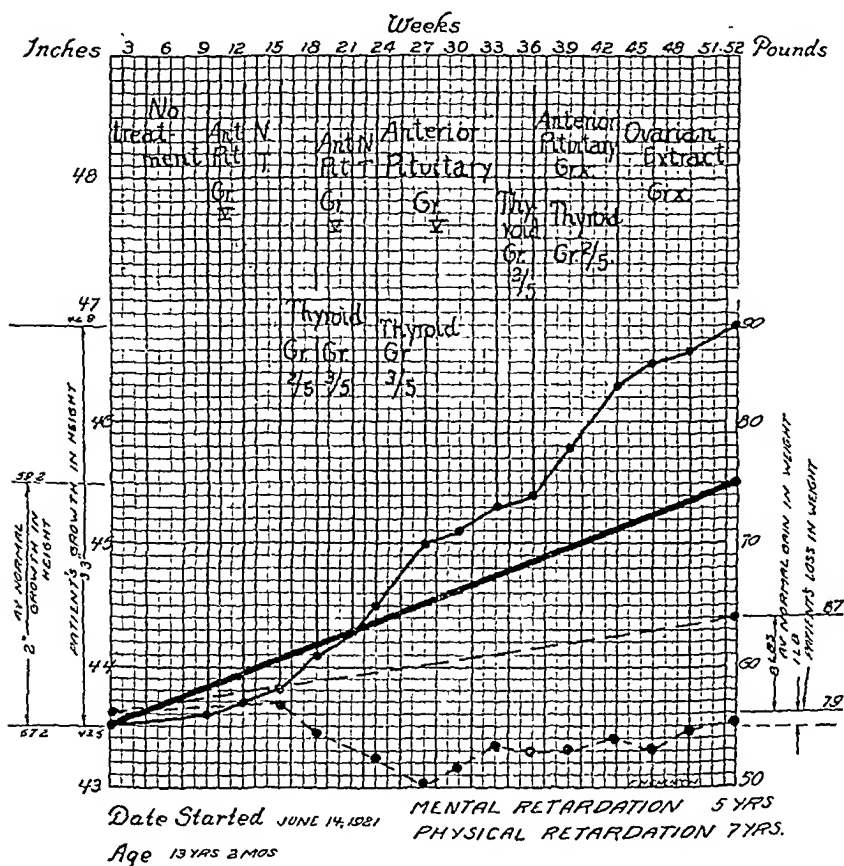
*Examination:* The patient came under observation when 13 4/12 years old. She was 45.5 inches high and weighed 56 pounds, a normal weight for a girl of 6 8/12 years, but 10 pounds overweight for her height. In fact, she was just a little shorter than her normal sister, age 6 (See illustrations). She had the typical skin,

facies, fat pads, etc., of the cretin. Her basal metabolism rate was moderately low ( $-18\%$ ). She had not matured. Her mental development was much retarded; when  $11\frac{4}{12}$  years old, her mental age was  $6\frac{8}{12}$  years. The Wassermann was negative. X-ray examination (Dr. M. W. Clift) showed an epiphyseal development of about 8 years. She had had some thyroid treatment, but none for several years.

*Treatment:* The child was under observation for 8 weeks without treatment, during which time she grew  $1/10$  inch, but did not

## ADAM CASE II CRETIN

### Height and Weight Chart for 52 Weeks



change otherwise. For 3 weeks she was given 5 grains of anterior pituitary extract daily, and during the next 3 weeks she received no treatment (See chart). In this 6 weeks' period she grew  $2/10$  of an inch, twice as much as she had without treatment. Then the thyroid was given alone for 3 weeks with a moderate gain in height, but when the pituitary was combined with the thyroid a really

remarkable growth followed. A drop in weight resulted from the thyroid feeding with a subsequent rise.

After 36 weeks of treatment the pituitary and thyroid were discontinued and whole ovarian substance substituted in an effort to stimulate the onset of maturity, but without result.

*Results of Treatment:* During the 6 years prior to treatment the patient grew 3 inches. During the 52 weeks of treatment she grew 3.3 inches, keeping pace with her normal sister. A better



CASE II--AFTER ONE YEAR'S TREATMENT

growth was made with the pituitary and thyroid than with either singly.

A marked change in disposition was also noted, a change from apathy to liveliness, although the Binet test did not indicate mental improvement. Her changed appearance may be seen by comparing the photographs. Treatment was discontinued during the summer of 1922, and at the end of that time the child had slowed up considerably. Her pulse was 70 and temperature subnormal, sure indi-

cations for further treatment. Three months' treatment restored her to nearly normal. She was then lost sight of for a year, until January, 1924, during which time she received no treatment. She was found to have returned to her former state of cretinism, looking exactly like her first photograph. Her skin was very rough and dry, her temperature subnormal and pulse slow. While during the year of treatment she grew 3.3 inches, during the year without



treatment she grew only 1.6 inches. She is now 16 years old, but has shown no signs of maturity.

### CASE III. M. N. CRETIN

*Family History* throws no light upon etiology.

*Personal History:* The patient was the third of 4 children; the others are normal. Her birth was normal, following a normal pregnancy. She grew well until 3 years old, then very slowly until 5 years, and not at all between 5 and 7 years. She was always well except for usual childhood diseases, but never matured.

*Examination* Her age was 14 9/12 years. She had the height of a girl of 7½ years. While she had retained the contour of a

child and no secondary sexual characteristics had appeared, she was somewhat obese. A large head, eyes far apart, saddle nose with nostrils pointing forward were noted. The skin was rough and dry, but the hair abundant and fine. Her temperature averaged 96.8 degrees and her pulse rate 74. X-ray plates (Dr. M. W. Clift) showed a normal epiphyseal development for her age, a very rare occurrence in a cretin. The sella was large and showed evidence



CASE III, AGE 15

of erosion. The plate of the skull suggested a slight increase of intracranial pressure. The patient was mentally competent, but very quiet and had little to say.

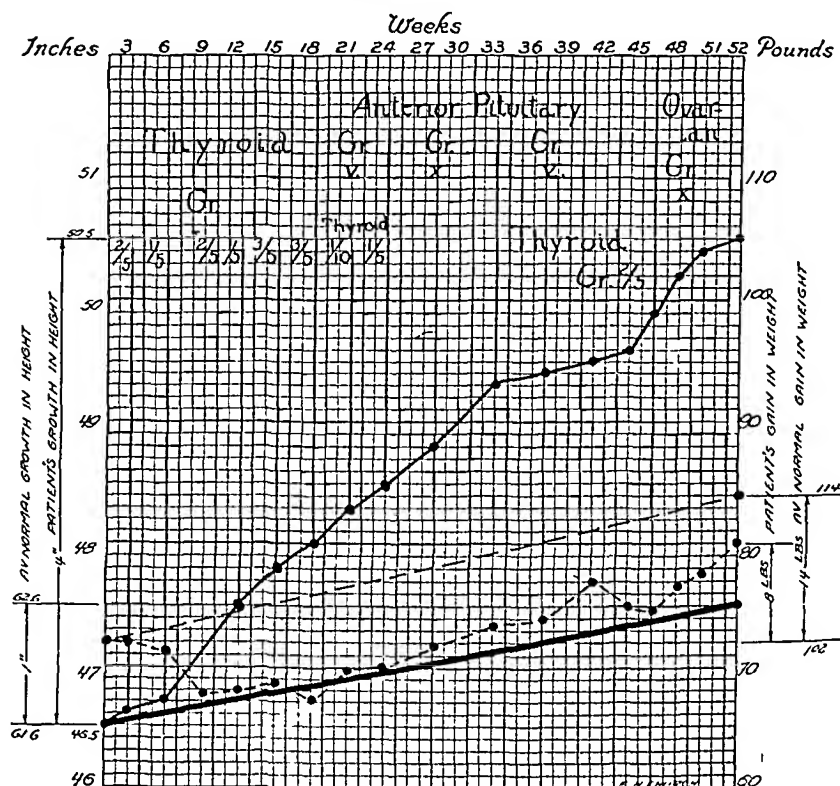
*Treatment:* This patient had never before received treatment. For 17 weeks she was given desiccated thyroid extract alone, during which time she grew 1.5 inches and lost 4 pounds in weight (See



chart). The dosage was kept very low, the patient receiving only 1/10 to 2/5 grains daily. Then for 7 weeks 5 grains of anterior pituitary extract was added daily. This did not increase the rate of growth. Then for 9 weeks she was given the pituitary extract without the thyroid, with a corresponding gain in weight, but no change in rate of growth. For 7 weeks the pituitary was reduced from 10 to 5 grains daily and the thyroid, 2/5 grain daily, added. Here there was noted a marked falling off in the growth rate. At the end of the first year the patient had grown 4 inches, the average growth for her age being about 2 inches a year. At the same time she

### MARGUERITE N. CASE III CRETIN

#### Height and Weight Chart for 52 Weeks



Date Started FEB 2, 1921

MENTAL RETARDATION NONE

Age 14 YEARS 6 MOS

PHYSICAL RETARDATION ABOUT 7 1/2 YEARS

experienced an entire change of disposition, becoming more alert and active in every way.

When the patient was 15 7/12 years old, having never menstruated, the thyroid and pituitary feedings were discontinued and 10 grains of the whole ovarian extract substituted in the hope that maturity might be stimulated. Eight weeks later her mother reported that the child had complained of cramps in the lower abdomen without intestinal upset. Examination revealed early breast develop-

ment and a few sprouting pubic hairs. Twenty-nine days later she had another attack of abdominal pains. These occurrences led to the expectation that the menses would soon appear but, although the secondary sexual characteristics steadily developed, the actual menses were not established for 10 months after the ovarian substance was first given. Now the menses apparently became regular and the cretinism seemed to be improving even more rapidly.

She was not seen again for a year (January, 1924), but during 9 months of that time she still took thyroid extract, but no anterior



CASE III--AFTER 15 MONTHS TREATMENT

pituitary or ovarian material. For 3 months she had had no medication. She menstruated only 3 times, the last several months ago. Her symptoms of cretinism had all returned; the pulse was 60 and the temperature 95 degrees. She had grown only 0.9 inches in comparison to the 4 inches per year while under treatment. The basal metabolism rate, however, was only -15. Renewed treatment will doubtless result in marked improvement.

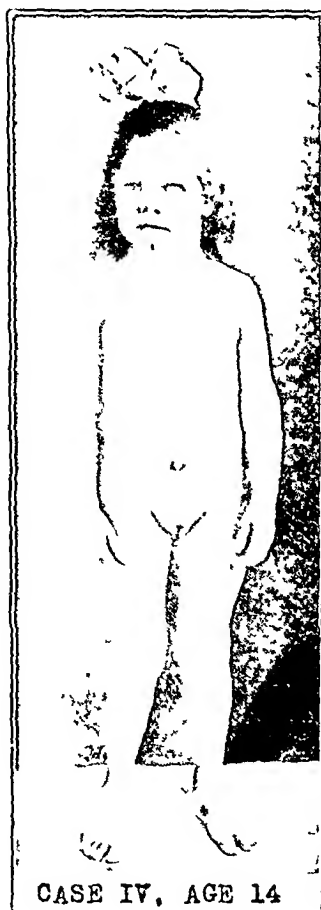
#### CASE IV. D. S. CRETIN

*Family History:* The patient has poor heredity. An aunt was insane and a brother feeble-minded. The parents were divorced.

*Personal History.* When 4 months pregnant the mother was operated upon for empyema. The patient was delivered at full term after instrumental labor; she was breast fed. During her first year

the child showed unusual apathy and suffered severely from constipation with hard, dry stools. She had dysentery when 1 year old. The condition of cretinism was recognized early, but thyroid was given only intermittently, never persistently.

*Examination* The patient came under observation when 13  $\frac{4}{12}$  years old. At this time her height was 42 inches, an average height for a girl of 5 years. She was 5 pounds overweight for her height. She had the typical facies and physical configuration of the cretin, resembling Case II in nearly every particular. Mental retardation was also a marked feature; when 13 years old, her mental age was only 6.



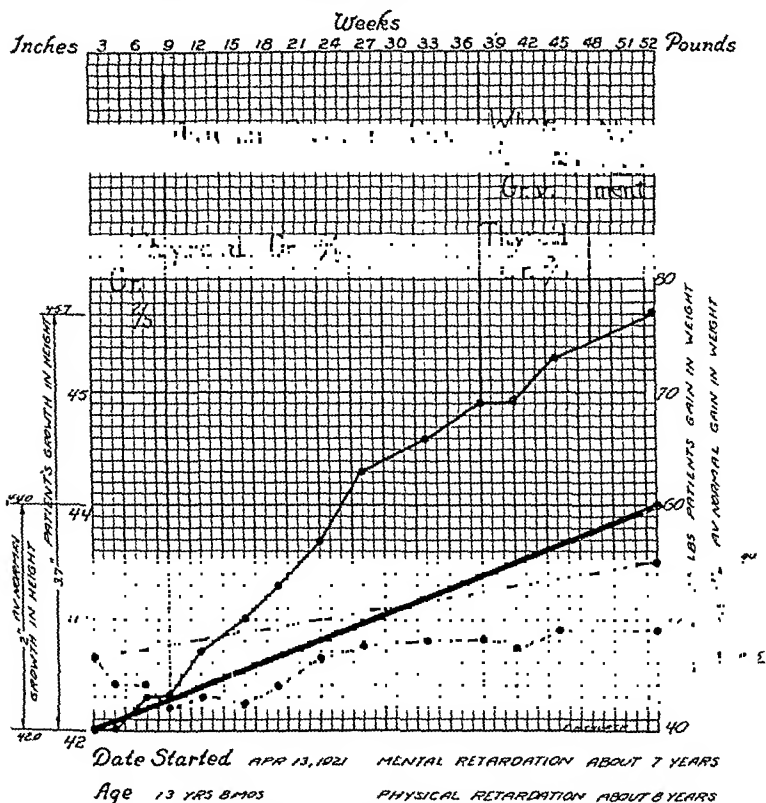
*Treatment:* (See chart.) Under thyroid extract alone for a period of 7 weeks, she showed little improvement. With the addition of anterior pituitary extract a marked increase in the growth rate began, and at the end of the year the patient had grown 3.7 inches, 1  $\frac{1}{2}$  inches more than is usual in normal children of her age. She also improved somewhat mentally and her skin and hair became less dry.

She was not seen again for 14 months (January, 1924). During this time she had no treatment. She had grown only 0.5 inches, a

contrast to the 3.7 inches grown during the year under treatment. She was now 16 7/12 years old and showed no signs of maturity. One see frequently in articles on cretinism the statement that the menses appear early. An authority such as Engelbach (1) says, "Their menses appear very early, at the age of 8 or 10, and are usually very profuse in amount and prolonged in duration, lasting from 4 to 6 days." The writer's experience has been just the contrary; in his cases menstruation has occurred, if at all, very late, at from 15 to 18 years, and very scanty.

### DORIS S CASE IV CRETIN

#### Height and Weight Chart for 52 Weeks



### CASE V. L. B. CRETINISM COMPLICATED BY RACHITIS

**Family History:** There is no history of goitre or cretinism in family. The patient was the second child of 6, of whom 4 are living and normal and 1 dead of scarlet fever.

**Personal History:** The patient was born after normal pregnancy at full term, with easy labor. She weighed 5 pounds at birth. Three days after birth she became jaundiced and remained so for 2 years. She did not sit up until 2 years old nor walk until 3½ years. At 5 years she could say a few words, but did not talk

until 7. Her tongue was never large, but the skin was harsh and dry and she suffered severely from constipation and enuresis. She complained of the cold a great deal.

This patient was examined at the University of Michigan Hospital 4 times over a period of 5 years, and I am indebted to Dr. D. M. Cowie for the following record: "Was 28/12 years when first



CASE V. ABOUT 3 YEARS OLD

admitted to hospital. She presented the typical appearance of sporadic cretinism and was put on thyroid extract. Second examination at 4 11/12 years. Much improved, could walk and say a few words. Thyroid continued. Third examination 5 years plus. Still improving. Fourth examination 7 11/12 years. Could now make simple sentences. Pituitary whole gland, grains 1 daily, added to thyroid."

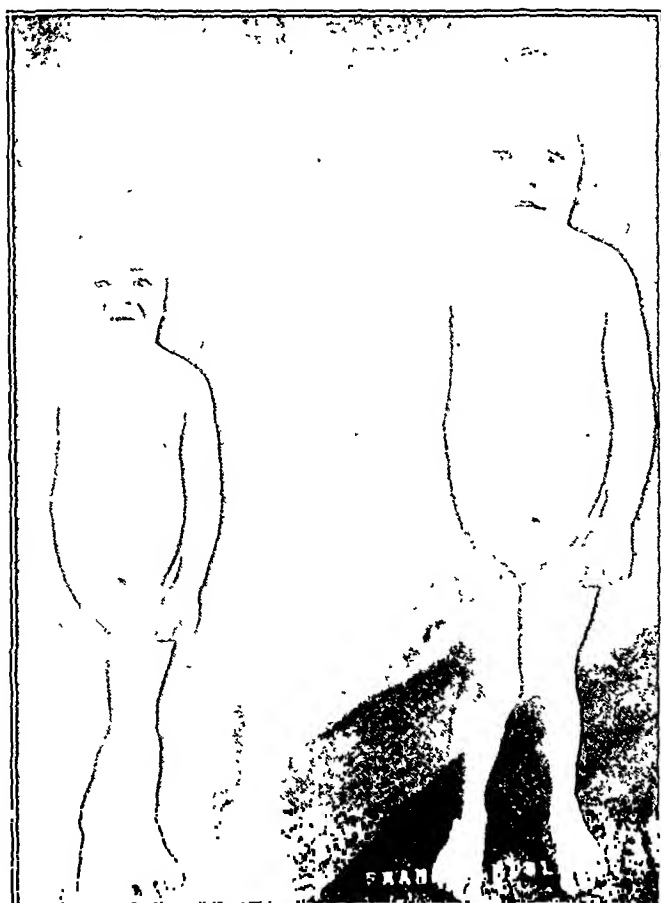
*Examination:* The patient came first under observation when 8 3/12 years old. She was 37.7 inches tall, the average height of

a child of  $3\frac{1}{2}$  years. Her appearance was that of a dwarf with cretinoid features. In addition, her face had a distinct senile look. Her *contour* was that of a rickety dwarf with pot belly, enlarged joints, etc. The *head* measured 20 inches, with low forehead, flatness at the back, but no bosses. Her *eyebrows* in the outer third were



sparse (Hertoghe's sign). The *skin* was harsh and dry, but not scaly. The *nose* was slightly saddle shaped, with nostrils pointing forward. The *thyroid* was not palpable. No second *teeth* had yet erupted. The *hands* were typically cretin, wrinkled, short and stubby. The *tem-*

perature was 99, the pulse 100 (She was still taking thyroid). X-ray examination (Dr. M. W. Clift) showed: Normal thickness of skull, with imperfect ossification around fontanelles; sella enlarged with posterior clinoid processes tilting backwards; no evidence of rachitis in bones of thorax or upper extremities, but marked irregularity and change in the density of the epiphyses of the heads of the femora.



CASE V, 8½ YEARS

The small figure gives patient's actual height; the tall figure what would have been her height if normal.

The enlarged sella suggested pituitary involvement; the cranial changes, cretinism; and the long bone changes (femur), rachitis.

*Treatment:* For 9 weeks she received daily 5 grains of extract of the anterior lobe of the pituitary. The next 8 weeks thyroid extract alone was given, and then for 15 weeks the two were combined.

*Results of Previous Treatment:* In 5 years on thyroid alone she grew 9½ inches, or at the rate of 1.9 inches per year. It is

only fair to say, however, that due to parental neglect there were intervals during which no extract was given.

*Results of Present Treatment:*

Nine weeks (anterior lobe alone), grew 0.5 inches=rate of 2.9 inches per year.

Eight weeks (thyroid alone), grew 0.7 inches=rate of 4.5 inches per year.

Fifteen weeks (thyroid plus pituitary), grew 1.1 inches=rate of 3.8 inches per year.

Growth for whole period (32 weeks)=2.3 inches=rate of 3.7 inches per year.

Unlike the preceding cases, a better growth was obtained on thyroid alone than on anterior pituitary alone. Treatment was now discontinued for 10 months, during which she grew only 0.6 inches, or at the rate of .072 inches per year, as compared with 3.7 inches while under treatment. Her weight increased 6½ pounds, and cretinoid symptoms, both mental and physical, reappeared.

*Discussion:* While the rachitic dwarf, where the dwarfism because of some hypothyroid symptoms to think that the thyroid is dependent upon a severe preceding rickets, is frequently seen, the combination of cretinism and rickets is much more rare. Gordon (2) in speaking of the hypothyroid child says that "constipation, deficiency in height and weight, enuresis and convulsions may at times, but not every time, be due to hypothyroidism. How much of the clinical aspect of rickets is due to deficiency of this gland is not known, but it seems plausible is a factor in the causation of this disease."

#### CASE VI. P. B.

##### PRE-ADOLESCENT HYPO-PITUITARISM (ANTERIOR LOBE ONLY), OR INFANTILISM OF THE LEVI-LORAIN TYPE.

This type is chiefly due to underactivity of the anterior lobe of the pituitary, the posterior lobe not being affected, and occurring before adolescence. Falta (3) says "Infantilism may be defined as a standing still at the infantile stages of development, considering especially the following facts: the genitalia and the *vita sexualis* remain undeveloped or develop deficiently; the same is true of the secondary sexual characters; the involution of the lymphatic apparatus is deficient, the growth is deficient, ossification and the closure of the epiphyses are delayed."

Beck (4) describes a case as follows: "Slender skeleton, skin soft and pale, large shoulders, lower extremities long and slender, trunk relatively small—absence of or slight secondary sexual characteristics."

*Family History:* The parents are both short, but normally developed. There is no history of glandular diseases in family.

*Personal History:* Pregnancy, birth and infancy were normal. The patient grew and developed normally until he was 13, when all growth and physical development suddenly ceased for 5½ years. Up to that time, when he was 18½ years old, he had developed no secondary sexual characteristics. Then his tonsils and adenoids were removed and within three months after the operation his voice changed, his genitals grew and pubic and axillary hair appeared. He



gained 10 pounds and grew a very little. During the second 3 months after the operation growth and development again came to a standstill. He was not mentally retarded. He consulted the writer because of his small stature and infantile development.

*Examination* The patient came under observation in 1916 when he was 18 9/12 years old. He was 60.6 inches high, about the average height of a boy of 13, and was slightly overweight for his height. The lower length of his body exceeded the upper by 13 inches, a childish proportion. He had a small slender bony framework, long

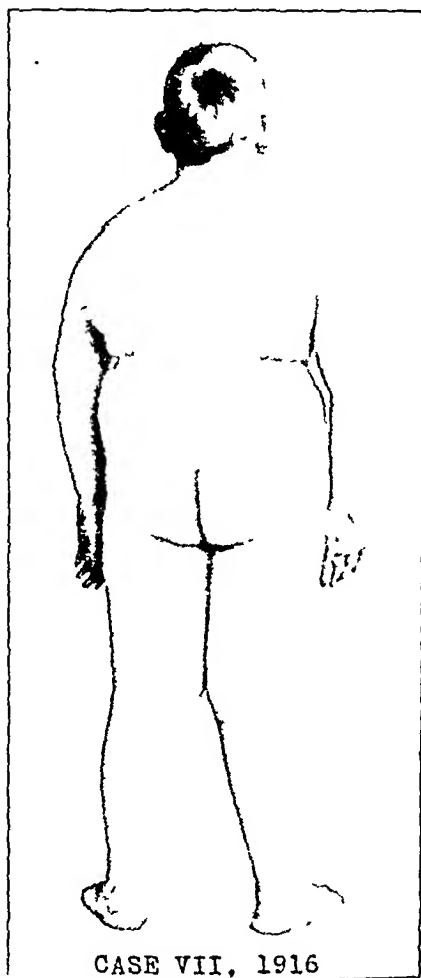
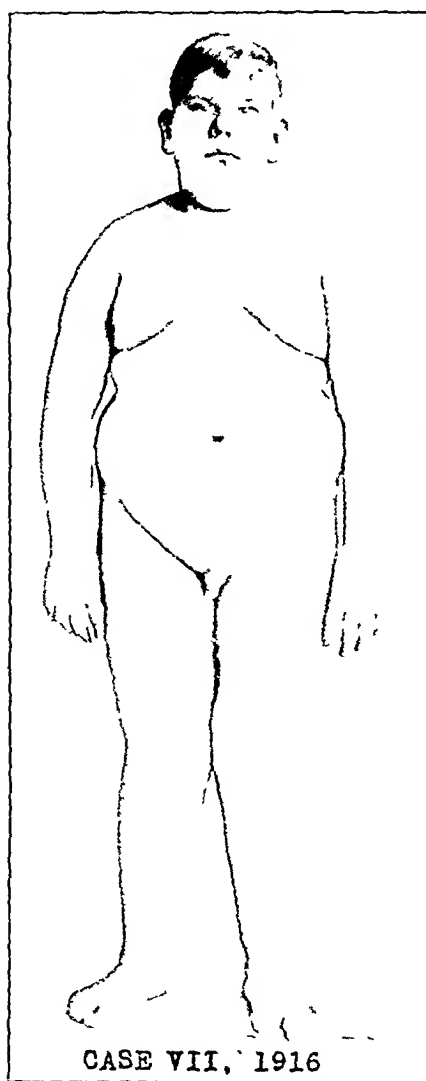


extremities for the length of his trunk and large shoulders. The genitals were small and the pubic and axillary hair scanty. X-ray examination (Dr. P. M. Hickey) showed a sella which was almost completely closed by the projection forward of the posterior clinoid processes upon the anterior. Plates of the epiphyses of the long bones showed that ossification was that of a boy of 14, a delay of 5 years.

*Treatment:* (See Chart 6.) It will be seen that in this case the patient apparently grew as well on a combination of suprarenal and thymus extracts as he did upon thyroid and anterior pituitary.



Another interesting point in this case is the history of sexual development, hitherto held in abeyance, starting after adenoidectomy. Bryant (5) in 1916 attributed the more rapid growth after adenoids had been removed to the mechanical stimulation of the pharyngeal pituitary, a body in structure analagous to the anterior lobe of the true pituitary. It is at any rate an interesting hypothesis.



#### CASE VII. A. W. DYSTROPHIA ADIPOSEGENITALIS

PRE-ADOLESCENT BILOBAR HYPO-PITUITARISM WITHOUT TUMOR.

*Family History:* American parentage. Parents both healthy, neither stout. Mother's brother was perhaps a hypo-pituitary case. Died suddenly, cause not given.

*Personal History:* The patient was the middle one of 3 children; the eldest is normal; the youngest has same type of obesity as the patient but without any other symptoms. Pregnancy and birth were normal. The patient was a very small infant and poorly nourished. He was breast fed  $1\frac{1}{2}$  years. He talked at  $1\frac{1}{2}$  and walked at 3. From the age of 18 months to 3 years malnutrition was marked. At 4 he had severe scarlet fever. This was followed by a polyuria which continued at intervals for 3 years.



Shortly after recovery from scarlet fever, he began to grow fat and has continued to increase abnormally in weight ever since. The following symptoms began with the obesity and continued to the time of observation: marked drowsiness in the daytime, falling asleep any time and anywhere; frontal headaches; enormous appetite. He had nocturnal enuresis for years. He was mentally retarded, when 14 years old having the mentality of a boy of 6.

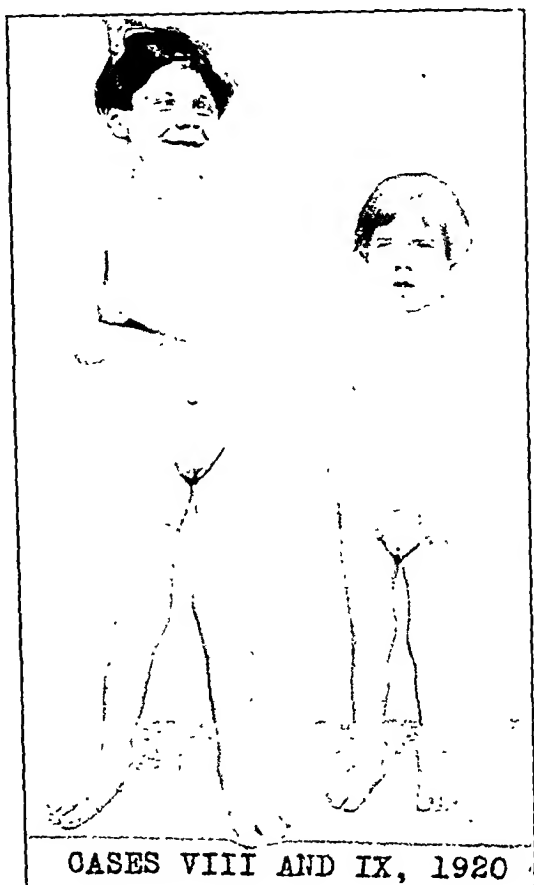
*Examination:* He was 14 years old when first seen and has been under observation for 6 years. He was an enormous boy bulging with fat. He had small "pig" eyes, large outstanding ears, and a happy expression. He smiled constantly when spoken to, but was somnolent when undisturbed. The weight was 186 pounds, nearly 100 pounds more than that of the average boy of his age. His height, 58.25 inches, was fairly normal. Stripped, he showed the typical distribution of fat of pituitary obesity. The fat was especially noticeable on mammae, abdomen and hips, while the extremities were comparatively lean. Although 14 years old, he showed no signs of sexual development; the scrotum was rudimentary, the testicles undescended and the penis small. He had marked genu valgum and flat feet. The hands were typical of pre-adolescent hypopituitarism, soft and narrow, the fingers wide at the base and tapering to a point. Temperature, pulse and blood-pressure were all within normal limits. The blood examination showed the marked relative lymphocytosis so often seen in glandular cases; in this patient 54%. X-ray examination (Dr. P. M. Hickey) showed a sella somewhat larger than usual, contrary to the ordinary finding in these cases, but was otherwise normal. As will be seen by reference to the photographs as well as to the text, this case presents an almost textbook picture of Froehlich's syndrome, with the sole exception of stunted growth usual to this type.

*Treatment:* For 8 weeks he was given whole pituitary by mouth in ascending doses from 10 to 40 grains daily. Only two changes were noted: his drowsiness disappeared; in fact, he became wakeful at night, and the enuresis ceased entirely. His weight increased 5 pounds and he grew 1.6 inches. He then began to suffer from attacks of severe abdominal pain; as this was probably due to excessive peristalsis from the large doses of pituitary, the latter was discontinued and thyroid extract substituted. So for the next 6 weeks he received thyroid alone in ascending dosage until he was taking 6 grains daily. For the next 13 weeks he received intermittently whole pituitary extract 30 grains and thyroid 6 grains.

At the end of 6 months' treatment, the patient had gained 13.25 pounds and grown 2½ inches (about twice as much as the average boy of his age grows during that time). He still complained of occasional headache, had the same distribution of fat and showed no signs of sexual development. At this point the war interrupted the observation, but an effort was made to provide a supply of extract for the patient and keep him under some sort of medical supervision. So all the following year he received more or less organotherapy, but no notes were available as to his progress.

The patient was then committed to the State institution for the feeble-minded at Lapeer, and in 1920, more than 4 years after treatment had been started, he again came under the writer's care. He was at this time 17 7/12 years old. As will be seen by the second illustration, a great change had taken place. His weight had decreased 3½ pounds, his height increased 2 inches. The chest measure was the same, but the waist measure was 2½ inches less. His features had changed most of all; formerly poorly developed, they now had an almost hyperpituitary cast, the supraorbitals and the maxillae being especially prominent. The axillary and pubic hair was now abundant, but the latter had the feminine distribution so noticeable in these cases. The genitals had developed, yet one testicle was undescended. The obesity, although still typical, was not as marked, and he had no subjective symptoms. On the other hand, he had made no progress in mental development.

*Discussion:* When one considers in how many instances infection seems to be an etiological factor in endocrine disorders (to cite a common example, the relation between quinsy and hyperthyroidism) scarlet fever at 4 followed by the syndrome of hypopituitarism is very suggestive of cause and effect.



CASES VIII AND IX. A. K. AND H. K. SISTERS  
PLURIGLANDULAR

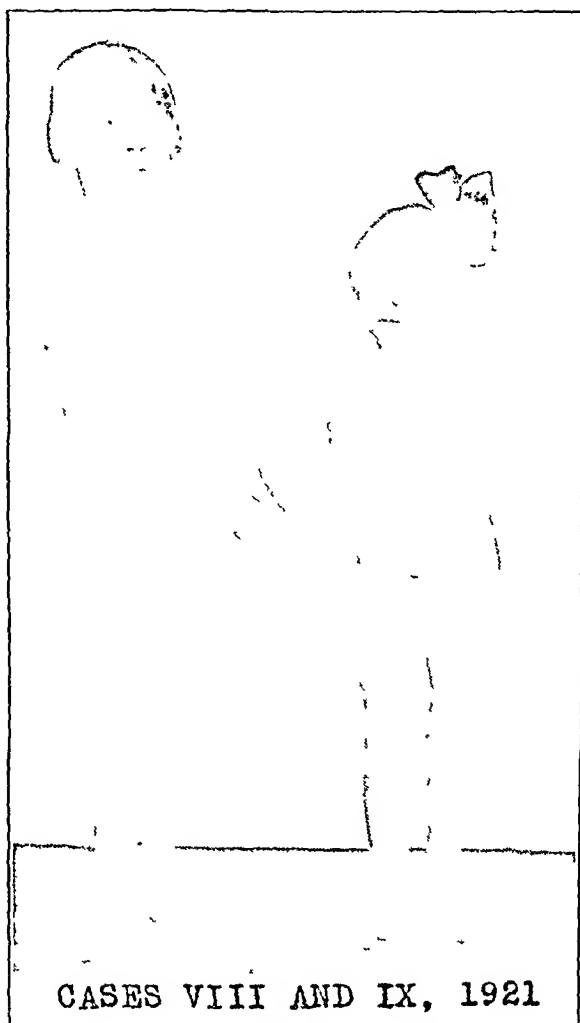
PROBABLY GENERAL GLANDULAR DEFICIENCY WITH THE ANTERIOR LOBE  
OF PITUITARY AND THYROID ESPECIALLY INVOLVED

*Family History:* Could not be obtained, but all 3 children of the family are feeble-minded. These cases were first observed in 1920 at the Michigan Home for Feeble-minded at Lapeer.

A. K., the elder, was 13 years old. The only history obtained was that the mother fell downstairs when pregnant. The child had

convulsions from 4 months to 1½ years. She could not stand until 5 years old, and then not without support. She never talked.

*Examination:* Although 13 years old, she had the height of a girl of 6, but was somewhat overweight for her height. She had a few of the characteristics of the cretin, especially the conformation of the face and the saddle nose with the nostrils pointing forward. Her hair was very coarse and black, resembling that of the Japanese. Yet the skin was fine and soft. The pulse rate and tem-



perature were normal. The most marked physical feature was the extreme weakness of the lower extremities. She could hardly stand alone, and when assisted in walking had a shuffling gait with the knees bent and the feet abducted and everted. Mentally she was of very low grade, being classified as an idiot.

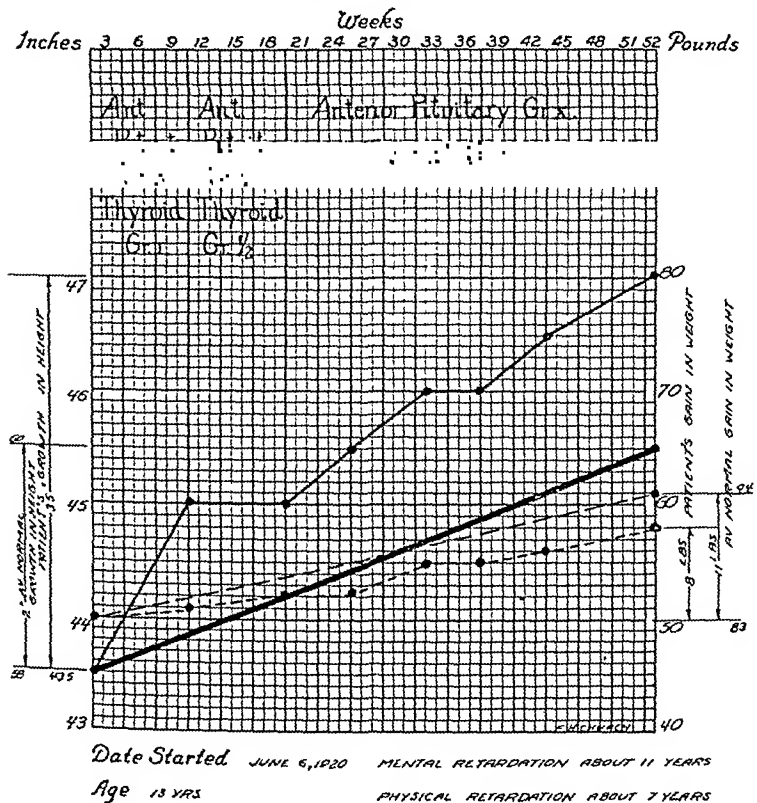
H. K., the younger sister, age 7, was of higher grade mentally than the elder and of better physical development. Yet she pre-

sented much the same physical signs as the elder, though all in lesser degree. She could walk slowly without help, although she was by no means as active as a normal child of 3, to which her weight and height corresponded.

*Treatment:* Two principal indications for treatment had to be met in these cases: first, anterior lobe deficiency as evidenced by retarded growth and, as Engelbach (6) has pointed out, by decreased muscular tonus; second, the hypothyroid condition. Parenthetically,

*CASE VIII                      ARNETA K*  
*RETARDED MENTAL<sup>20</sup> PHYSICAL DEVELOPMENT*

*Height and Weight Chart for 52 Weeks*



the writer wishes to say that practically all his glandular deficiency cases receive small doses of thyroid extract routinely along with other indicated therapy because there seems to be no question, clinically, that thyroid extract speeds up or acts as a whip to the rest of the endocrine chain.

So both children were given anterior pituitary and thyroid extracts for over a year (See charts 8 and 9). Both children made quite remarkable growth records. The elder grew  $3\frac{1}{2}$  inches in





*Past History:* She is oldest of 3 children; the others are normal. Pregnancy, infancy and early childhood were normal. In 1914, when she was 8 9/12 years old, the Germans invaded her native village and drove the inhabitants out. During the whole period of the war she lived in the open with little shelter and food. In addition, she was in constant terror. As a result, her growth entirely ceased and her development partially, as described below. She became very nervous and is now (1921) only becoming more calm. During the war her voice became husky and she has never regained full use of it.



*Examination:* Her general appearance was that of a dwarf with mature face and expression. It was difficult to determine her mental age, as her English was too limited to permit a Binet test.

When first seen she was 16 5/12 years old. Her height was 49.7 inches, the average height of a girl of 9. *This was her age when the war began.* Her weight was 65.5 pounds, 8 pounds overweight for a child of 9. While her contour was rather broad for her height, she still retained the figure of a child. She never matured, there were no secondary sexual characteristics. Her face,

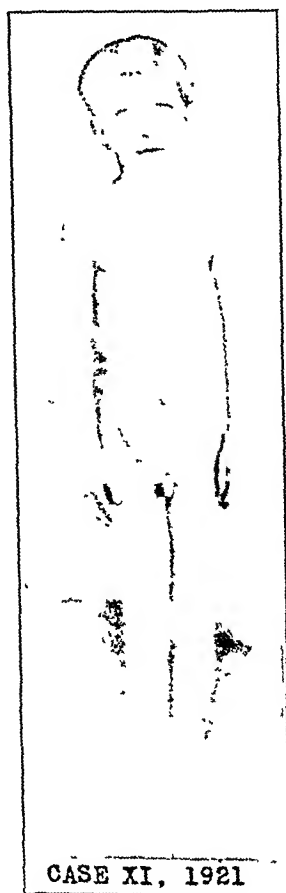
was rather overdeveloped and her expression suggested a greater age than 16. There was a marked spacing of the upper and lower central and lateral incisors. She had a small goitre of the colloid type and a fine, slight tremor of the hands but, except for a persistent tachycardia, no other symptoms of hyperthyroidism. Her heart showed a mitral stenosis and her pulse rate was high, averaging 120 to 130.

*X-ray Examination* (Dr. M. W. Clift) showed a normal sella and epiphyses open throughout.



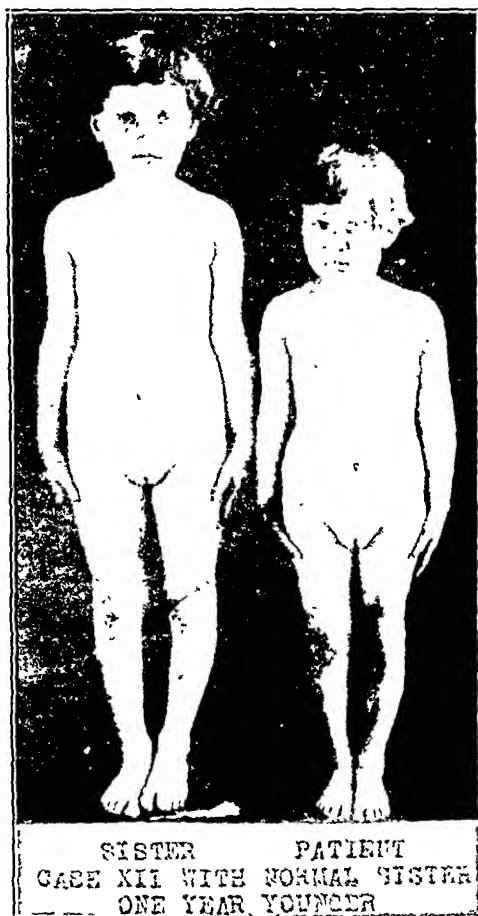
*Treatment:* On account of the rapid pulse and other symptoms suggestive of hyperthyroidism, she was given anterior lobe extract exclusively. She received 10 grains a day for 18 weeks. At the end of that time she had grown only 0.4 inches and her weight remained the same. She was in better general health, but showed no signs of maturing. Treatment was then discontinued for 6 weeks, and then she was put on 10 grains of ovarian substance a day in the hope of stimulating sexual development, but this was entirely without effect.

*Discussion:* A definite endocrine diagnosis presents certain difficulties. Emotional disturbances such as grief and fear are well-known forerunners of exophthalmic goitre. Her tachycardia, nervousness and tremor all point to hyperthyroidism. (Unfortunately a basal metabolism estimation was not available.) On the other hand, the thyroid acts as a stimulant to



growth and development instead of having a retarding influence, yet the endocrine disturbance in this case resulted in marked retardation in growth and in sexual development [See Uhlenhuth (7)].

history than by any present signs. The symptoms point to anterior lobe disturbance and not to posterior lobe involvement, as do the cases reported in the literature. Is it not possible that an infantile hydrocephalus resulted in more or less permanent degenerative changes in the anterior lobe and accounts for his present symptoms? But we are now in the realm of theory and not of fact! It should be added that as usual other glands were secondarily affected, in this case the thyroid especially.



#### CASE XII. S. L. RETARDED GROWTH

THE RETARDED GROWTH THAT CHARACTERIZED THIS CASE WAS  
PROBABLY DUE TO TRUE DWARFISM

*Family History:* The parents are Russian Jews. There has been no similar case in the family, nor does the family history throw any light upon the etiology.

**Personal History:** The patient is the second of three children; the other two are normal. Pregnancy and labor were normal. A sister 1 year younger is much taller than the patient (See illustration). The child was very small at birth, but well-formed and healthy. Except for the usual childhood diseases she has always been well. Mentally she is slightly above normal. She was brought for examination only because she did not grow.

**Examination:** At 8 10/12 years she was 39.2 inches tall, a trifle less than the average height of a girl of 5 years. Her weight of 32 pounds made her somewhat underweight for her height. Physical examination showed a moderate tachycardia, a somewhat retarded dental development and an epiphyseal retardation of about 18 months. There were no stigmata of endocrine deficiencies and, with the above slight exceptions, the child was perfectly normal except as to size.

**Diagnosis:** The diagnosis at the present time is doubtful, and only time can determine it. If when she reaches the age of puberty she matures normally both as to menstruation and the secondary sexual characteristics, but has not materially increased in stature, she may be classed as a *primordial* or *true dwarf*, that is a miniature woman, normal except as to size. If, however, she fails to mature and retains the childish characteristics beyond the age of puberty a diagnosis of *infantilism* would be probable.

**Treatment:** As might be expected from the lack of glandular symptoms, organotherapy had little effect. She was under observation for 76 weeks; during this time she received 44 weeks of treatment, being without treatment for 32 weeks. Under treatment she grew 1.2 inches, or at the rate of 1.4 inches per year. Without treatment she grew 1 inch, or at the rate of 1.6 inches per year, or slightly more without treatment than with it. The normal average rate of growth for a girl of her age is 2 inches per year.

### CASE XIII. S. G. RETARDED GROWTH

#### THE RETARDED GROWTH IN THIS CASE WAS PROBABLY DUE TO TRUE DWARFISM

**Family History:** Although the parents are of normal height, there is a history of dwarfism in the family; the maternal grandmother was only 50 inches tall.

**Personal History:** The patient was the last of four children, the next older being 17 years older than patient. His father was 49 and mother 47 when the patient was born at full term after a normal pregnancy. His weight was 6 pounds at birth, but he grew very slowly from that time. He was breast fed for 1 year. He walked at 18 months and talked at 1 year. His health has been generally good except for an attack of influenza followed by otitis media. For several months before coming under observation, the mother noticed a limp of increasing severity. The patient is active mentally and well up to his age in school work.

**Examination:** The patient was 7 6/12 years old. He was very small for his age, with delicate limbs, hands and feet, but rather large head. There were marked dorsal scoliosis and pot belly with corresponding lordosis. The teeth were poorly developed and in bad condition. Otherwise the patient was physically normal.

Normal height for age 47.4 in.	Normal weight . . . . . 52 lbs.
Patient's height . . . . . 34.6 in.	Patient's weight . . . . . 28 lbs.
Underheight . . . . . 12.8 in.	Underweight for age.. 24 lbs.

**Treatment:** He was referred to an orthopedist, Dr. F. C. Kidner, for spinal treatment, which was successfully carried out by

means of a plaster cast. For  $2\frac{1}{2}$  years he was given small doses of thyroid with anterior pituitary extract. The treatment was carried out with only about 4 months' intermission altogether. At the end of that time his record was as follows:

Normal height for age  
(10 years) ..... 51.9 in.  
Patient's height ..... 39.3 in.

Normal weight ..... 65.4 lbs.  
Patient's weight .... 37 lbs.

Underweight for age 28.4 lbs.

Underheight ..... 12.6 in.

His height corresponded to that of a child of  $3\frac{7}{12}$  years old.



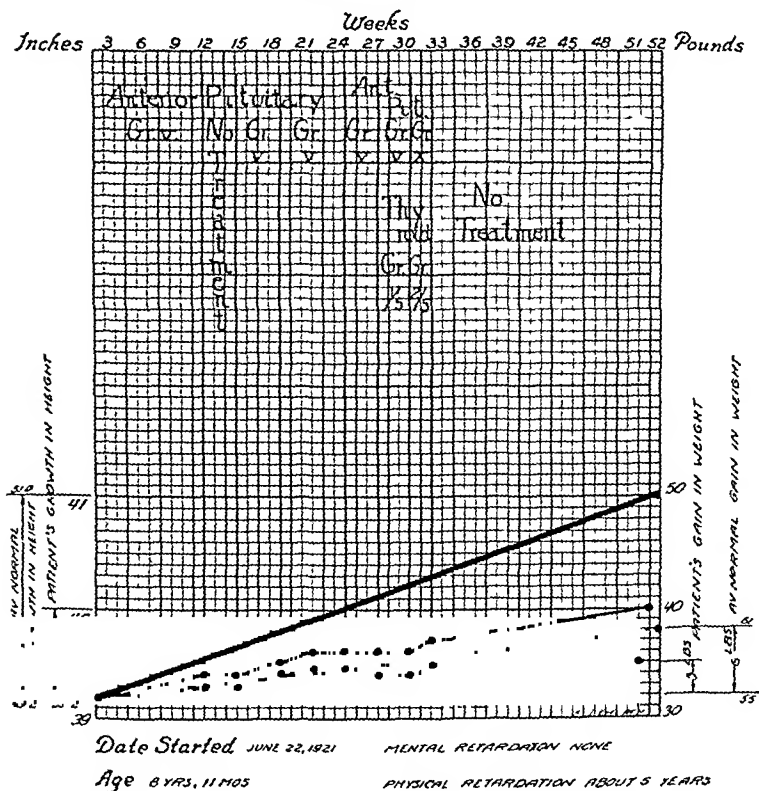
CASE XIII.

*Discussion:* This case is very similar to the preceding one. His very small stature, the lack of definite endocrine symptoms, the lack of response to treatment and the history of dwarfism in the family all suggest a diagnosis of a true or primordial dwarfism.

Hausemann (10) describes primordial dwarfs as individuals who at birth already present small size, who will go on growing but always remain smaller than normal individuals of the same age. They arrive at the termination of development at the same age as normal persons, therefore the epiphyseal sutures ossify at the right time. Aside from their small size, these individuals

### SADIE L CASE I RETARDED GROWTH

#### Height and Weight Chart for 52 Weeks



shows no abnormal psychic or somatic conditions. Their intelligence is normal and sex maturity is attained.

Cases XII and XIII, in the writer's opinion, fulfill the requirements for the diagnosis of true or primordial dwarfism.



## CASE XIV. RETARDED PHYSICAL GROWTH

THE RETARDATION IN THIS CASE PROBABLY DEPENDED UPON THE INFLUENCE OF HEREDITY. J. D. CAME FOR TREATMENT FOR STUNTED GROWTH ONLY

*Family History:* Although of American nationality, small stature was frequently met with in his family. The paternal grandfather was the tallest member, being 70 inches in height. The paternal grandmother was 61 inches; the maternal grandfather, 59 inches; the maternal grandmother, 61 inches. The father is 67.8 inches, mother is 61 inches tall. No history of endocrine disease in family was elicited.

*Personal History:* Is negative as far as endocrine or other diseases are concerned. The patient was a strong infant and weighed 32 pounds when 2 years old. There is no record of previous heights.

*Examination:* The patient is normal both physically and mentally except for marked underweight as detailed below. Careful investigation could elicit no reason for this underweight. When first seen he was 15½ years old and weighed and measured as follows:

Normal height for age . . . . . 63.9 in.	Normal weight . . . . . 114.2 lbs.
Patient's height . . . . . 62.6 in.	Patient's weight . . . . . 94.5 lbs.

Underheight . . . . . 1.3 in.	Underweight . . . . . 19.7 lbs.
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*Treatment:* On account of underweight it was thought best not to give the patient any thyroid extract. For 11 months he received 10 grains of anterior pituitary extract daily for 3-week periods with 1-week intermissions. His record was then as follows:

Normal height for age	Normal weight . . . . . 124.7 lbs.
(16 5/12 years) . . . . . 65.6 in.	Patient's weight . . . . . 112 lbs.
Patient's height . . . . . 66.5 in.	

Over average normal height . . . . . 0.9 in.	Underweight . . . . . 12.7 lbs.
----------------------------------------------	---------------------------------

In the 11 months of treatment he grew 3.9 inches, the normal growth for that time and age being only 1.7 inches. Also his weight, though still deficient, became nearer normal. He is now in the best of health.

*Discussion:* A normal boy, showing no endocrine symptoms except retarded growth, responded markedly to the growth stimulus of anterior lobe of the pituitary feeding. A sister, 17 years old, and only 60 inches in height, was also brought for treatment, but since the x-ray plates showed that the epiphyses were entirely united, treatment would have been useless and was not attempted. Carpenter and Ferguson (11) reported 14 cases of naval cadets treated by thyroid and anterior lobe extracts for stunted growth and concluded that "growth is not stimulated by thyroid and pituitary therapy in individuals at or near chronological maturity." However, since 12 of the 14 cases showed closed epiphyses, making further growth impossible, the conclusion seems hardly a fair one.

## THERAPEUTIC SUGGESTIONS:

1. Before starting treatment use every means possible to make a diagnosis. A careful physical examination from an endocrine standpoint supplemented by x-ray and laboratory investigations should be given each patient. This sounds like very elementary advice, but unfortunately it is too often needed. Many physicians seem to practice organotherapy in an entirely hit or miss manner, a direct result of the pernicious influence of the commercial houses putting out pluriglandular mixtures.

2. While each deficiency case is usually pluriglandular, one gland generally stands out as primarily and chiefly affected. Treat this deficiency first by administering solely the animal extract of that gland; then if necessary add, one at a time, the extracts of the glands secondarily affected to the prescription.

3. Do not prescribe the pluriglandular mixtures of the mail-order houses. Each case must be studied and prescribed for separately. Besides containing extracts which are of no use to your individual patient, the dosage of those extracts that the patient does need is rarely suitable. "Shot-gun mixtures" of the "ready-made" variety are not good therapeutics.

4. It does not matter much what brand of extract is used, provided it is potent, for, like digitalis, there are both potent and impotent extracts on the market and only experience can determine which are which. The method of preparation and the freshness of the product usually determine its potency. The ideal method, but not usually possible for the practitioner, is to have the extract specially prepared in small quantities from very fresh glands.

5. Dosage: As so many elements enter into the determination of proper dosage for an individual case, no definite dosage suitable to all cases can be given. It is the writer's opinion that too large doses of thyroid are usually prescribed and too small doses of the other glands. It is best to intermit the administration of glandular extracts, giving them for three weeks, for instance, then stopping them for one.

6. Do not expect immediate results. Persevere with the organotherapy and do not give up a case as hopeless until at least three months of uninterrupted treatment has been given. Unless there is some good reason to change the extract or the

dosage, at least three weeks should elapse between changes of prescription.

The pituitary and suprarenal extracts used in these cases were for the most part freshly prepared in the Research Department of Parke, Davis and Company. The process used was the simplest one possible in order that no active principle might be lost, especial attention being paid to the retention of the lipoids which are usually removed in the preparation of most of the commercial extracts. While it is rather difficult to arrive at definite conclusions regarding the comparative value of different glandular preparations, the writer has treated so many cases with both the freshly prepared extracts and the commercial preparations purchased on the market that he feels justified in saying that better results were obtained with the former.

The writer wishes to acknowledge his indebtedness to Dr. E. M. Houghton and the Research Department of Parke, Davis & Company for liberal supplies of these extracts for experimental purposes. Thanks are also due to Dr. H. A. Haynes, Superintendent of the Michigan Home and Training School at Lapeer, and to Miss Bertha Giffen of the Department of Special Education of the Detroit Public Schools, for referring many of the patients.

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## A CASE OF DIABETES. REFRACTORY TO INSULIN, RELIEVED BY ANTILUETIC TREATMENT

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F. S. (240446), colored, male, fifty years old, occupation butcher, was admitted to the medical service of the University Hospital, Sept. 24, 1923. His chief complaint upon admission was dizziness and polyuria. His family history was essentially irrelevant. He had been a heavy user of alcoholies during his entire adult life. During March, 1923, he cut his finger while butchering. Following this he developed a gangrene which necessitated the amputation of the finger by his family physician. During the summer prior to his admission he noticed that he drank great quantities of water in an attempt to satisfy his thirst, that he had a ravenous appetite and an excessive excretion of urine. His polyuria developed to the point that he dribbled urine between his frequent urinations. He also noted some edema of the feet, body and face, which was transient. He was informed that he was suffering from diabetes mellitus and advised to enter the hospital. He had received no treatment for his diabetes prior to admission.

Physical examination upon admission revealed evidence of marked pulmonary tuberculosis involving both lungs and posterior cervical adenitis. His pupils reacted sluggishly to light and accommodation. He gave no history of venereal infection. Laboratory examinations revealed a moderate leucocytosis with 74 per cent polymorphonuclear leucocytes, normal erythrocyte count and diminished hemoglobin. His Wassermann reaction at this time was negative. Sputum examination showed the presence of acid-fast bacilli. Blood sugar was 500 mgm per 100 cc and urine sugar, 2.2 per cent.

The day after admission he was placed upon a diabetic diet. He was kept on this diet for 4 weeks with periods of starvation. At the end of this time his blood sugar was 460 mgm. and urine sugar, 0.5 per cent. He was then given insulin, beginning with

three units, three times daily. This was gradually increased until after a period of four weeks he was receiving thirty-four units of insulin (Lilly) three times daily. During this period of insulin treatment his blood sugar ranged between 450 and 500 mgm. per 100 cc. and his glycosuria disappeared. For the following ten days the insulin treatment was discontinued and the patient kept upon his routine diabetic diet. At the end of this period his blood sugar was practically the same as it had been, but his urine sugar rose to 4.8 per cent.

At this time, Nov. 16th, 1923, his blood Wassermann was found to be positive two (Craig). The following day he was given an injection of neosalvarsan and potassium iodid by mouth and mercurial inunctions were started. For three days following this, his urine was sugar free. Upon Nov. 26th his urine sugar was 2.5 per cent. Antiluetic treatment was continued for three more weeks, at which time his urine became sugar free and his blood sugar fell to 140 mgm. per 100 cc. Upon a diabetic diet he remained at this level until his death from a pulmonary hemorrhage Dec. 25th, 1923.

*Autopsy* was performed the following day. The diagnosis of tuberculosis was confirmed. The findings in general included nothing apparently pertinent to the immediate interest of this paper except in case of the pancreas. On gross inspection this organ was found somewhat large, but otherwise showed nothing noteworthy. Upon microscopic section the first survey disclosed nothing out of the ordinary, the glandular structures being arranged in the usual manner and showing little evidence of degeneration. Upon more careful examination the Islands of Langerhans were found to be almost completely lacking. In a few places groups of partially degenerated cells were seen. The degenerated areas were not fibrous but showed granular necrosis. For these details regarding the autopsy findings I am indebted to Dr. E. Scott.

## A CASE OF POSTOPERATIVE MYXEDEMA

E. BONILLA and C. BLANCO SOLER

MADRID, SPAIN

Postoperative myxedema is rare, since usually only part of the thyroid is extirpated, which at most results only in slight thyroid insufficiency. Kocher states that total extirpation of the gland causes severe myxedema in 70 per cent of the cases; Socin and Garre, 50 per cent; Reverdin, 40 per cent; and Trombetta, 27 per cent. Nine out of 38 cases of postoperative myxedema studied by Kocher were of light form. The low percentage of postoperative myxedema is due to the existence of accessory thyroids which spontaneously hypertrophy (cases of Wolffmann and of Reverdin). This syndrome seems to occur most often in goiter regions.

Sometimes extensive partial thyroidectomy causes similar syndromes, but of a less serious nature (12 cases of Reverdin). In modern literature we find very few cases. Munk (1) has seen myxedema in a woman 19 years of age who had well marked hyperthyroidism a short time after extirpation of only the left lobule. Faber (2) has observed in a young woman who was operated upon two years previously for goiter, a clinical picture exhibiting ascites, cephalalgia, and loss of hair. Ascites was produced after each of eleven punctures. Talma's operation was performed and Faber found at laparotomy that the liver and other abdominal organs were in perfect condition. Ascites and the other symptoms disappeared after the employment of thyroidin, and Faber believes that in this patient ascites was a symptom of hypothyroidism analogous to the thyreoprivic edema described by Eppinger. Möbius (3) reports myxedema in a man 36 years of age who had been operated upon for goiter and in whom good results were had from thyroidin. Myxedema usually appears immediately after the operation, but occasionally, as in the case reported by Faber, not until after some time has passed.

Mackenzie (4) and Cordua (5) have observed myxedema produced by radiotherapy. The latter reported the case of a woman 38 years of age who had all the classical symptoms of Graves' disease. After five x-ray treatments she showed marked improvement, but later there was falling of the hair, diminished sweat, typical symptoms of myxedema in the skin, and intense melancholy. Thyroid opotherapy afforded great benefit, but did not affect a complete cure.

### CASE REPORTED

The case observed by us is as follows. R. R., aged thirty, a sergeant, had suffered a typical attack of Basedow's disease; there was mild goiter with exophthalmos, the signs of Moebius, Graefe and Stellwig were positive; there was tachycardia up to 150 pulsations, trembling, insomnia, diarrhea, great restlessness and nervousness, and great emotionalism. The right lobule of the thyroid, the isthmus and all of the left lobule except the posterior border were removed, the left side of the inferior thyroids being ligated. We saw this patient for the first time shortly after the operation. He then presented diarrhea, frequent and at times severe; light, nervous dyspnea; tachycardia, varying between 95 and 105 pulsations; trembling of the hands and the tongue; exophthalmos; cephalalgia; insomnia; light melanoderma; buccal pigmentation; asthenia; sexual frigidity; and intense melancholy with fear of being alone and a tendency to suicide.

The urine was normal. The blood pressure was 140 and 70 mm., respectively. The leucocytic formula was: lymphocytosis, 26; monocuclears, 3; polynuclears, 68; eosinophilia, 1; transitional forms, 2; total, 100. Blood sugar was 0.94 per cent, ascending after the injection of a miligram of adrenalin to 1.1 per cent (Bang's method); alimentary glycosuria was negative. The hyperthyroid syndrome persisted in spite of subtotal thyroidectomy. The cervical sympathetic chain on the left was then extirpated. After a few months the patient exhibited a clear myxedematous syndrome and since that time he has been under our care for more than a year. The myxedematous facies was typical (Fig. 1), though the coarseness of features suggested acromegaly. The pulse rate was 80 to 85 and constipation had succeeded the former diarrhea. The psychic symptoms became aggravated; exophthalmos persisted with a slight trembling; he became heavier, weighing 74.25 kg. One miligram of adrenalin caused intense local and light general reactions. Arterial pressure that had been 150 mm. increased in ten minutes to 170 mm.; the venous pressure remained at 110 mm.; there was no change in the pulse rate; the trembling was accentuated and became rather general. In spite of the fact that the patient objectively appeared exceedingly emotional there was no subjective emotional reaction (6).

Injection of atropin brought about a paradoxical result. The pulse rate decreased from 84 to 62, although no general disturbance was produced, and did not again reach 80 until two or three days later. Escudero (7), in 22 out of 304 subjects which he submitted to injections of atropin, encountered the same paradoxical result.

No satisfactory explanation can be found for this result and we are not warranted in accepting the theory that small doses of atropin are a transitory stimulant to the terminals of the vagus.

Basal metabolism was minus 10 per cent (8).

We now began an intensive thyroid treatment (six tablets daily of 0.3 centigrams). During a month of this treatment the patient was much improved, although the emotional symptoms persisted, and the exophthalmos diminished considerably. The basal metabolism

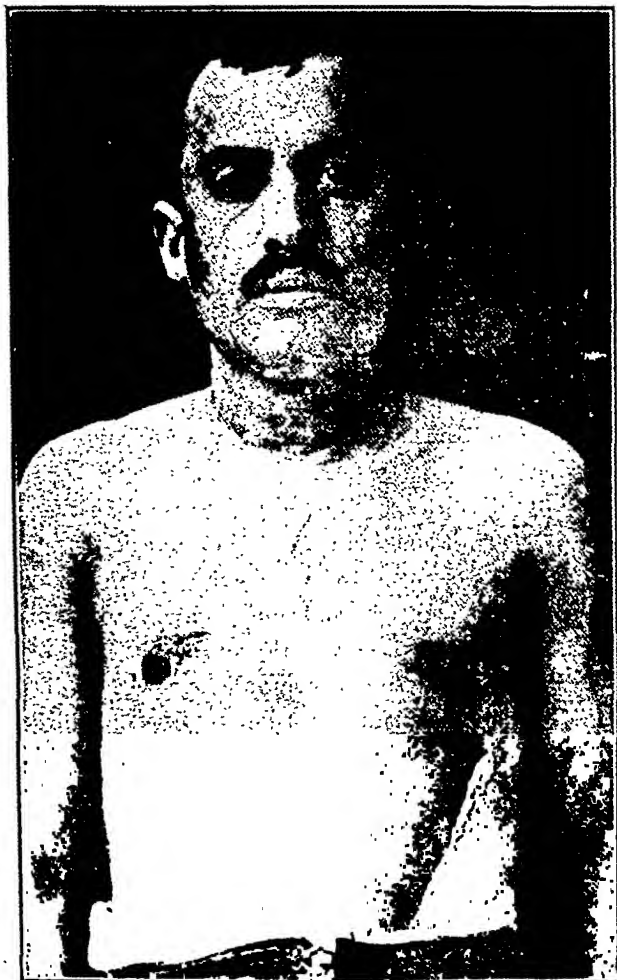


Figure 1.

was then plus 27 per cent, and the weight 71 kg. We therefore diminished the dose of thyroid, the patient taking during the first week only a single tablet daily; the second, two; the third, three;



and the fourth week, four daily. He constantly improved and we decreased the dose from two to one tablet daily according to his weight, which varied between 60 and 62 kg. Ultimately, in view of the patient's weight having fallen to 58 kg. and the metabolism being plus 25 per cent, he is taking one tablet every other day. The patient is now considered as completely cured, the psychic disturbance, which was the most rebellious symptom, having absolutely disappeared.

From a study of this case some interesting deductions may be made. In the first place, we have concluded that except in cases of compression, cardiac alterations, or other disorders in which social conditions act as impediments, hyperthyroidism ought always to be treated medically (9). Partial extirpation of the gland scarcely ever cures hyperthyroidism. Major resection, lately advocated by Els (10), ought to be discontinued absolutely.

We ought also to note that in our patient exophthalmos persisted after thyroidectomy and resection of the sympathetic, and that he was completely cured by thyroid treatment. Surgeons have called attention to the rebellious nature of this symptom; in 25 per cent of the subjects with hyperthyroidism operated upon by Kocher and considered by him as cured, the exophthalmos did not disappear, but its cure by thyroidin shows that it is sometimes a symptom manifested by thyroid hypofunction. Gley (11) reported in a rabbit a state of myxedema with exophthalmos following thyroidectomy, and from this single observation he denied the hyperthyroid pathogeny of exophthalmos. This theory is not borne out, however, by the experience of this clinic, nor is it in accordance with our ability to produce exophthalmos experimentally by feeding thyroid extract (12); without doubt, however, exophthalmos can be produced by excess of retrobulbar fat or perhaps, as Goldscheider supposes (13), by venous ecstasis or edema of the retrobulbar tissue, thus explaining its cure by thyroidin. Marañón and Carrasco have cited the case of an obese woman who had arrived at the menopause and whose case had been diagnosed as Graves' disease. She presented marked exophthalmos; her basal metabolism was minus 15 per cent. Thyroidin was administered and two months later her general condition was much improved and exophthalmos had almost disappeared.

The case presented by us has also the value of an experimental fact in favor of stimulating opotherapy, recently so severely criticized by Gley (14). The French authors (Hallion, Carrion) call this a variety of substitution opotherapy. They attempt to activate the function of a gland that is deficient by the employment of small doses of its extract, little by little, until its physiological limit is reached.

This type of therapy is undoubtedly valid, for, as Marañón (15) says, we have all seen cases of thyroid insufficiency in which after administration of thyroidin (at times an exceedingly small amount) we observe definite disappearance of the symptoms, indicating that the cure is not owing to the substitute and timely action, but to the stable recuperation of the functional tone of the gland. The therapeutic hyperthyroidism produced by small doses of thyroidin is another factor in favor of this theory.

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## OVARIES AND MENSTRUATION

ELISEO RAMIREZ, M. A. S. I. S.

MEXICO, D. F.

The question as to whether the corpus luteum plays any part in initiating menstruation has been much debated. During the years 1918 and 1919 opportunity was offered to study the problem personally. The results were published in 1920. In the course of operations performed during menstruation it was found that the ovary contained no corpus luteum. On the other hand, at operations performed on women during the inter-menstrual interval these bodies were found. In three cases, on the other hand, in which the corpora lutea were extirpated in the course of operations for displacement of the uterus, there appeared within three to five days a hemorrhage that seemed to be normal menstruation. The phenomenon, however, is not constant in its occurrence.

Space does not serve for an adequate review of the literature, but an observation by Ochsner, of interest in this particular connection, may be cited. This writer has observed that when the corpus luteum fails to undergo its normal physiological regression in the ovary of the cow the animal becomes sterile and her condition may be compared to that of a woman afflicted with amenorrhea. Surgical extirpation of the corpus luteum in such cases restores fecundity.

Not only does the corpus luteum have no function in initiating menstruation, but its presence impedes the menstrual onset. I have been able to demonstrate an antimenorrhagic action of extract of corpus luteum in cases of hemorrhage of ovarian origin. Moreover, in women the duration of the active corpus luteum before its regression begins is three weeks, which is precisely the length of the intermenstrual period.

To Leo Loeb (1) we owe the knowledge that the corpus luteum produces modifications of the uterine mucosa proper to conception. He has shown that it so sensitizes the uterine mucosa as to permit the formation of pseudodecidua when artificial mechanical stimuli are applied. Nielsen (2) and I have also

shown that irritation of the uterine mucosa by a foreign body only gives origin to placentomas when the ovary contains corpora lutea.

The complicated morphological details of the intermenstrual uterine transformations have been described among others, by Hitschman and Adler (3), and more recently by Ramírez (4). In these changes the whole mucosa is involved. The changes include hyperplasia, hypertrophy, twisting of the glands and other modifications which indicate the beginning of the post-menstrual stage, acquiring their maximum development in the premenstrual epoch. In each one of the phenomena I have pointed out elsewhere the direct relation with the immediately preceding and with the state immediately following.

By the time the corpus luteum has arrived at its involutional stage there have appeared in the uterus characteristic modifications in the case of women as well as other mammals. None of these changes, however, constitutes an essential part of menstruation, which is not determined by the corpus luteum, the mission of this organ being that of effecting the transitory changes preceding this activity.

In collaboration with Ochoterena (5) I have made a careful study of the formation of lipid bodies by the interstitial cells of the ovary. This work was briefly reported in an earlier issue of this JOURNAL. If the lipid products of mitochondrial origin which we have described, and which are coexistent with the menstrual period, pass into the blood stream, it was thought that their presence might be demonstrated.

With the collaboration of Juan D. Terecero of the Military Hospital, the action of the serum upon the uterine mucosa was thereupon determined by the method of Abderhalden. The uterine mucosa was prepared by following the technic described by this author for placenta. When soluble products no longer were obtained the fragments were preserved in toluene. To proceed with the reaction the uterine fragments were placed in small dialyzing sacs that had been previously proved impermeable to Witte's peptone and white of egg. There was then introduced into the sack blood serum obtained by venipuncture from a woman at intervals during menstruation. Dialysis into distilled water at 34 degrees was carried out and the dialystate tested both with ninhydrin and the biuret reactions. It was found that

the reaction was always positive when the blood was taken during the menstrual period and negative in the interval. These results were confirmed by Abderhalden and lead to the conclusion that during menstruation there exists in the blood the products of the interstitial gland of the ovary, which have a cytolytic action, especially on the uterine mucosa. These experiments suggested the hypothesis that the cytolytic products, after affecting the uterine mucosa, were expelled in the menstrual flow. The destruction of the mucosa tested *in vitro* was observed to be directly similar to that seen *in vivo* during menstruation and estrus.

Sterilized linen cloths used during the menstrual flow were reduced to small fragments and placed in a sterilized flask containing 1500 cc. of ethyl alcohol. This, after filtering, displayed a beautiful amber color. Evaporation at 40 degrees C. quickly caused the appearance of turbidity, and when the evaporation was concluded a residue was left in the form of small, yellow, opaque, fatty scales.

With a small part of these scales microchemical reactions have been carried out with the following result: They took on an obscure maroon color with the tetroxide of osmium. Sudan III gave no color. With acetate or chloride of zinc heated in acetic solution it did not give a red color corresponding to cholestrum until it was diluted to 1:80,000.

Rejecting that which had been reduced in acetate deprived of fatty acids in order to avoid pain when injected, a complete solution was not yet obtained, but a part remained in suspension; this was deposited upon standing and it therefore became necessary to place in the flask glass pearls and agitate it. My collaborator further prepared ether extracts and precipitated them by means of acetone, but he has used them solely for the study of their physiologic action.

For the study of their action and with the object of controlling the cause of perturbations of ovarian origin, my students, Anastasio Vergara and Gerardo Varela, administered some of this extract to two rabbits, giving me the following account of their investigations:

"We procured a rabbit from the physiological laboratory weighing 3.30 kg., eight months of age, it having been isolated since its last litter to make sure it was not pregnant. During two weeks we observed the physiological constants, then made a median lapa-

rotomy. The horns of the uterus presented a reddish color, cylindrical form and the part near the vagina had a circumference of 2 cm. Two days afterwards we performed total ovariectomy and after two more days we commenced subcutaneous injections of 1 cc. of the extract. The injections were continued daily during the following ten days, after which they were abandoned. The horns of the uterus were found to be of paler color than before, and on gross view slightly less aplastic, measuring 2 mm. in circumference. As a control we procured another non-pregnant rabbit of the same litter weighing 3.34 kg. Total ovariectomy was performed. The uterus was 23 mm. in circumference, the rest of the characters being normal. After 12 days we found the uterus of a yellowish rose color, its horns aplastic, somewhat flattened and less in circumference by 3 mm. In both rabbits we obtained cicatrization by first intention. We took for study various portions of the uterine horns, dividing them transversely into segments of 3 to 4 mm. These were placed during 24 hours in potassium bichromate, 3% in 80 parts, and osmic acid, 2% in 20 parts. They were then cut in paraffin at 5 micra and stained by diverse methods, among which was the eosin-wasserblau method of Ochoterena, which gave exquisite differentiations.

"Microscopic study showed considerable atrophy of the middle tunica with the characters which Hegar, Sokloff, Gottschalk (6), and Beuttner and Jentzer (7) have described as sequels of castration. Certain details which are considered to be of interest will be considered later."

In this connection the mechanism of uterine atrophy should be considered. Okintschitz (8) reported the different modifications of uterine atrophy, following castration, provoked by injections of different ovarian preparations (Poehl).

Thirty-one animals were used. It was found that the uterine horns three months after castration were reduced to about one-half in both length and breadth. Injections of the total ovarian extract caused cessation of the atrophy almost completely. The extract of corpus luteum alone did not impede the atrophy, while ovary deprived of corpus luteum moderated the atrophy slightly, but did not greatly impede it.

Considering only the gross features in the light of the foregoing, it would seem that the injection of menstrual extract did not modify the course of the atrophy, but a study of the uterine mucosa showed a very interesting phenomenon.

The histological preparation (e. g., that shown in Fig. 1) was from a transverse cut from the middle of the uterine horn of a rabbit that had not been injected. The cut included the elliptical section, the largest diameter of which was 5 and the smallest 3 mm. The thickness of the wall at the point opposite the insertion of the broad ligament was 1.1 mm. The epithelium was beautifully preserved; the elements were identified singly; the protoplasm preserved its normal coloring; there was no

evidence of vacuolization nor of degeneration; the nuclei retained their membrane; the chromoplasm formed a delicate network; the basal membrane was distinct. The epithelium was continued in the glandular tubes, where it was possible to observe in one element or another secretory activity. The mucosa presented its classic aspect, forming plasmatic bundles of Robin. Among its elements were migrating cells, but not a single red

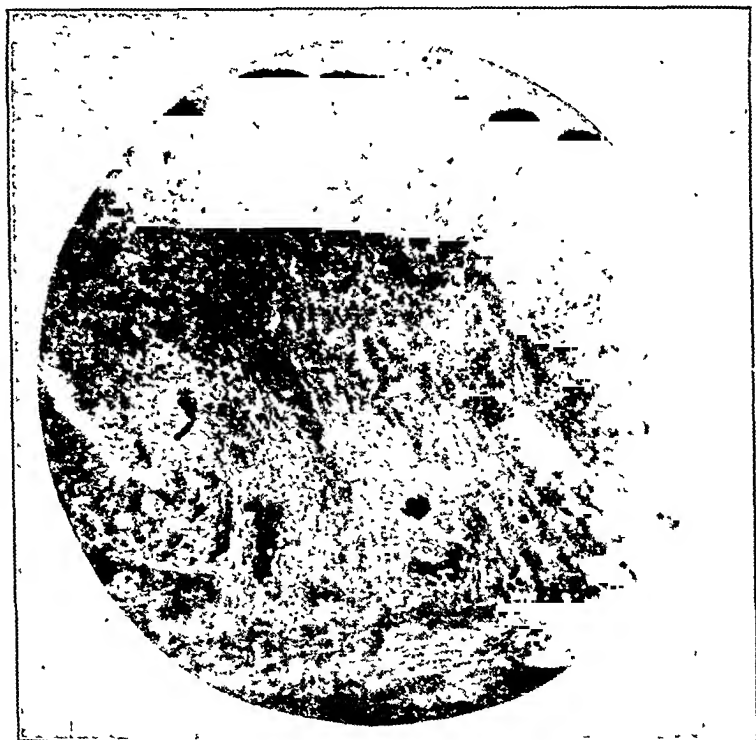


Fig. 1. Transverse section of the uterus of the castrated rabbit. Shows the process of atrophy.

corpusele, as we observed when filling the tubes. In contact with the middle tunic the submucosa showed gradations of atrophy which in the muscularis reached a maximum. In short, the muscular structures showed the changes characteristic of castration, whereas the mucosa and uterine glands took on the characteristics seen in normal estrus.

The preparations from rabbits injected with menstrual extract were in marked contrast with those of non-injected cas-



trated rabbits. Microscopic examination showed that there was *no epithelium covering any part of the surface*. The mucosa formed broken fringes, not limited by a basal membrane, but in rare and small portions its elements resembled cellular accumulations without fixed direction and about to separate. The functional part of the mucosa is formed by violet stained elements which swim about in an inundating sanguineous lake; the

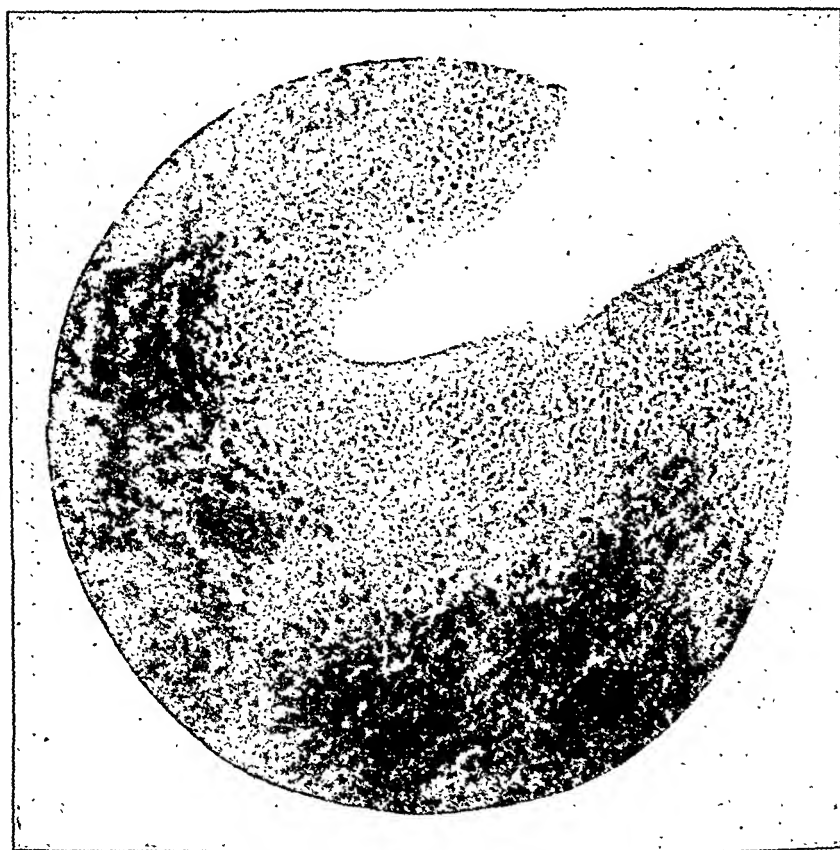


Fig. 2. Transverse section of the uterus of the rabbit castrated then injected with extract of menstrual fluid. In the depth of the fold of the mucosa the epithelium is preserved; from this new epithelium is regenerated.

red corpuscles have been able to pass the uterine cavity owing to the absence of the covering epithelium. The vessels are intact at the bottom but ruptured nearer the surface, allowing their contents to escape.

The microphotograph, Fig. 2, shows that only in a few places small columns of cells persist, suggesting an outline of a gland.

The deeper spongy zone of the middle layer shows like alterations of atrophy to those of the former preparation.

These experiments have recently been repeated with five other rabbits that gave similar results.

#### CONCLUSIONS

In seven rabbits castrated it was found that characteristic atrophy of the muscularis of the uterus occurred. The mucosa was well preserved. Lipoid extracted from the menstrual blood of women did not arrest the atrophy following castration in the rabbits, but led to *destruction of the superficial mucosa, the separation of the epithelial elements in the submucosa and intense sanguineous inundation*. The alterations produced are much like those that occur in the uterine mucosa of women. From previous studies it is believed that these experimental estrual changes are due to a lipoid produced by the interstitial cells of the ovary, carried to the uterus and discharged into the menstrual flow.

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# Editorial

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## INCIDENCE OF DIABETES

A correspondent has recently called attention to two abstracts in the November issue of *ENDOCRINOLOGY* which seem to reinforce a commonly held opinion that diabetes is more prevalent in the male than in the female sex.

For the registration area of the United States, at any rate, the incidence is notably higher in the male sex. In "Mortality Rates, 1910-1920" (pages 88-89), recently published by the Department of Commerce, Bureau of Census, U. S. A., it is shown, for instance, that in 1920 the adjusted death rate from diabetes was 15.9 per 100,000 for males and 21.0 for females of all ages.

Other interesting facts are that the rate for the colored race was 7.9, whereas for the white race it was 16.8. Whether this is due to racial peculiarity or, as seems to be the case in India, to differences in diet incident to differing economic status, presents an interesting problem.

Diabetes in the registration area of this country has been constantly increasing for the past 30 years. For all ages, among the males the rates for the decades ending in 1900, 1910 and 1920, respectively, were 10.8, 15.0 and 15.9; in females the rates were 10.1, 17.9 and 21.0.

There are also some interesting differences in the death rates in different states. For example, the range varied in 1920 from 5.8 in Mississippi to 23.5 for New Hampshire and New York.

—R. G. H.

## A NEW USE FOR PITUITRIN

In the world-wide paean of praise of the wonderful new addition to our therapeutic armamentarium, insulin, a single note of dissatisfaction has run. This is a warning of danger from which so potent a remedy could scarcely be free. The danger is hypoglycemia of a degree resulting in discomfort

or even death. Two correctives of insulin hypoglycemia have been used from the first, namely, adrenalin and glucose. Through the researches of Burn (1) a third antidote has now been made available, namely, pituitrin.

That adrenalin and pituitrin should have a similar effect on insulin hypoglycemia is surprising in view of the discovery reported by Stenström (2) that infundibular extracts suppress adrenalin hyperglycemia. This finding Burn has confirmed. It might be assumed, therefore, that pituitrin would act additively with insulin in further reducing the blood sugar.

Burn's work was done on rabbits in which the reactions to insulin had been carefully determined. For example, to a rabbit having a blood sugar of 121 mg. per 100 cc., 12 mg. of insulin was administered. Forty minutes later the blood sugar had dropped to 64 mg. and after 150 minutes it had reached the dangerous level of 36 mg. Four cubic centimeters of Burroughs, Wellcome "Infundin" was then administered, whereupon the blood sugar soon rose to 80 mg. It was found that the antagonistic effect of pituitary extract on insulin hypoglycemia is more extensive, more persistent and much more rapid in onset than that of adrenalin. That the pituitrin effect is not merely an example of non-specific reaction to tissue extractives was shown by the negative results secured when extracts of anterior lobe of pituitary, of spleen, thyroid, brain tissue or thymus were injected. Similarly, histamin, a very common component of tissue extracts, gave negative results. The method by which pituitrin antidotes insulin hypoglycemia presents an interesting problem for further study.

—R. G. H.

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# Book Reviews

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ENDOCRINE DISEASES. Wilhelm Falta. Trans. & Ed., Milton K. Meyers. 3d ed. P. Blakiston's Son & So., Philadelphia, 1923.

To write an acceptable treatise on clinical endocrinology in the present state of our knowledge presents a difficult task. As compared with other books in this field, Falta and Meyers have achieved a marked success. Meyers, in his capacity of editor as well as translator, has much enhanced the value of the book, both by the addition of new material not available when the original German edition was published and of numerous judicious and critical comments.

As is common in cases of books of this type, its strength lies in the clinical portion and its weakness in the biological introduction. Contrary to the statement of the editor, endocrinology has by no means followed the lines of development indicated by Falta's earlier beliefs. A large proportion of the Viennese theories have been discredited and the remainder have signally failed in the primary function of a theory, namely, to accommodate existing facts. The feature that most appeals to the reviewer is the differentiation between fact and theory. Dubious material is generally introduced by such phrases as, "it seems," "it may be that" or "it is probable." If the clinical readers would substitute for the first sixty pages of this book, which are largely concerned with physiology, either Vincent's or Shaffer's treatise, they would have in the remainder probably the most satisfactory treatment of the subject now available.

—R. G. H.

REJUVENATION AND THE PROLONGATION OF HUMAN EFFICIENCY. Paul Kammerer. Boni and Liveright, N. Y., 1923. Pp. 252.

This might be called a book of "blurbs." On the jacket the publishers and principal characters vie with each other in distribution of fulsome commendations. The book itself carries out the same general spirit. The author has performed the disservice to science and to Prof. Steinach of appealing from his medical-scientific peers to the uninformed populace. That the great body of level-headed clinicians is unconvinced of the value of the Steinach operation no one would suspect from anything

in the book unless, perhaps, its general air of over-anxiety to make out a strong case. Insulin was accepted everywhere within a year. Rejuvenation will be accepted quite as speedily when the evidence in its favor is equally sound and concordant.

That vasoligation may have some value is not denied. That endocrinology offers promise of considerably prolonging life and efficiency the reviewer happens to believe, but a book made up of premature ecstasy and skewing of evidence such as the one under discussion can only be deplored. That much interesting and sound information is included is, in this connection, beside the point. The book is not one suitable for readers who have not the necessary technical information to evaluate it. Its principal effect will probably be to arouse undue hopes in the minds of lay readers and give further lease of life to the monkey gland joke.

—R. G. H.

DIABETES-STUDIER. Karl Petrén. Gyldendalske Boghandel, Nordisk Forlag, Copenhagen, 1923. 956 pp. 8°.

An extensive review (in Swedish) of the results of the author's personal experiences with diabetic subjects during the last 10 years, describing especially the dietetic treatment used. For a summary of the subject matter see "Studies on Diabetes," by Petrén, page 189, in this issue.—R. G. H.

THE CHEMICAL BASIS OF GROWTH AND SENESCENCE. T. Brailsford Robertson. Monograph on Experimental Biology. Ed., Loeb, Morgan and Osterhout. J. B. Lippincott Company, N. Y. & Lon., 1923. 389 pp.

The present fad in biology is to fit formulas to facts or facts to formulas. On the other hand, the mathematical sea contains many rocks and cross-currents of which the amateur biological mathematician should be wary when he attempts to pilot his biological craft into harbor. This book of Robertson's is an exemplification of how to fit facts to formulas, or rather to a formula with its expansions. The formula is basically that for an autocatalyzed mono-molecular chemical reaction, which the author many years ago utilized in his interpretation of growth. The expertness with which this formula is handled should be a source of interested amazement to the uninitiated. Whether the generalized application of this logarithmic expression and its derivatives and the conclusions and speculations derived therefrom by the author will be accepted by biologists who are study-

ing growth is a matter for the future to tell. At any rate, workers in this field can be thankful to Robertson for giving them a starting point for discussion and for the compilation into one volume of so many valuable references. The rôle of the endocrine glands in growth are briefly mentioned, except with respect to the anterior lobe of the pituitary, a structure more familiar to the author by virtue of his own intensive studies on tethelin.

—F. S. H.

# Abstract Department

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Effect of acetylcholin, pilocarpin, atropin, potassium chloride, adrenalin, calcium chloride and nicotin on bile excretion in the dog with gall-bladder fistula (Beobachtungen über die Wirkung von Acetylcholin, Pilocarpin, Atropin, Kaliumchlorid, Adrenalin, Calciumchlorid und Nicotin auf die Gallenausscheidung am Gallenblasenfistel-Hunde). Adachi (A.), Biochem. Ztschr. (Berl.), 1923, 140, 185-202.

After the injection of 0.2 to 0.5 cc. of 1% adrenalin solution there was a quick inhibition of the flow of bile from the fistula in a fasting animal.—F. S. H.

The adrenalin chloroform syncope (La syncope adrénalino-chloroformique). Bardier (E.) & Stillmunkès (A.), Arch. internat. de pharm. et théér., 1923, 27, 375-414.

In this long paper there are one or two novel points. The authors state, for example, that adrenalin produces fibrillation of the ventricle in any stage of chloroform anesthesia—contrary to the opinion of Levy and others, who believe that it occurs only in light chloroform anesthesia. Of more interest is it that they find that quinine prevents fibrillation of this type, though the dose of quinine requisite is too large to enable it to be of use therapeutically.—Physiol. Abst., 8, 446.

The rôle of the adrenals in vitamin-B deficiency (Die Rolle der Nebennieren bei Mangel an Vitamin B). v. Beznak (A.), Biochem. Ztschr. (Berl.), 1923, 141, 1-12.

Pigeons were used and records made of the weights of the thyroid, pancreas, adrenals, liver, brain, heart and stomach together with determinations of the adrenin content of the suprarenals. It was found that the adrenals increase from one to two times the normal size in conditions of experimental beri-beri. The body weight as well as the weight of the pancreas, thyroid, liver and stomach decreases. The bulbous remains constant in weight in inanition and comparing the adrenals with this structure it was found that they increased in proportional weight from 3.4 to 9.6%. The hypertrophy of the adrenals is not attributed to the inanition, since when pigeons are allowed to starve to death on an insufficient diet of yeast the glands do not enlarge. The enlargement is therefore



attributed to lack of vitamin B. The adrenin content of the suprarenals did not increase but rather tended to decrease. The cause of beri-beri is therefore not associated with an increase in adrenin production.—F. S. H.

**Biophysical studies of the effects of various drugs upon the temperature of the brain and the liver.** Crile (G. W.), Rowland (Amy F.) & Wallace (S. W.), *J. Pharmacol. & Exper. Therap.* (Balt.), 1923, 21, 429-442.

A few of the drugs studied changed somewhat the temperature response of adrenalin as established in the normal animal. In the presence of morphin the temperature response of the brain is diminished in direct relation to the depth of narcosis; in the presence of strychnin a characteristic rise in the temperature of the brain and a fall in the temperature of the liver is produced which is followed by a fall below that produced by alcohol alone.—G. E. B.

**The clinical importance of the determination of sensitivity to adrenin.** Csépai (K.), Fornet (B.) & Tóth (K.), *Wien. Arch. f. inn. Med.*, 1923, 6, 383-394.

The sensitivity to adrenaline as indicated by blood pressure determinations may be of considerable diagnostic and prognostic significance. In goiter, Basedow's disease and hyperthyreosis there is an increase in sensitivity to adrenaline injected intravenously, while with simple goiter there is no increase in blood pressure over that shown by normal individuals on adrenaline injection. This simple procedure might well replace the determination of basal metabolism in such cases. In Addison's disease and diabetes insipidus there was a decreased sensitivity to adrenaline. The subcutaneous injection of adrenaline is also of value in myxedema as indicating the effect of thyroid administration.—Chem. Abst., 17, 3712.

**Adrenalin content of the adrenals after irradiation by x-rays.** David & Hirsch, *Klin. Wchnschr. (Berl.)*, 1923, 2, 790.

There have been various reports concerning the action of roentgen rays on the adrenal bodies. One group of observers found definite changes in the blood pressure, another group found changes in the sugar metabolism following radiation. Still another group could find no definite results. The authors studied the adrenalin contents in guinea pigs, rabbits and dogs, 40 in all. In each one, one adrenal body was isolated and exposed to the rays, which were of a definite quantity, while the other adrenal was thoroughly protected from the rays. The application of rays varied from one skin dose to one-fourth skin dose. Conclusion by the authors are as follows: (1) the adrenal system is influenced by radiation with x-rays; (2) a distinct lessening of function is obtained by a radiation of one skin dose; (3) an increased function is obtained by radiation with one-fourth skin dose.—*J. Radiol.*, 4, 376.

The importance of the adrenal glands in the action of certain alkaloids. III. Physostigmine on the blood picture. Edmunds (C. W.) & Putman (C. L.), J. Lab. & Clin. Med. (St. Louis), 1923, 9, 45-53.

The authors have previously pointed out that the adrenal glands may play a distinct rôle in producing some of the changes in the body following the injection of certain alkaloids, eminently pilocarpine and strychnine. In this paper the effect on the blood of dogs of injections of physostigmine is reported. The authors conclude that the drug of itself, produces no increase in the number of white blood cells in the circulating blood. The leucocytosis following the injections is really due to the increased amount of epinephrine because of stimulation of the adrenals by the physostigmine and is absent if the adrenals are removed before the physostigmine is given. Injections of strychnine produce analogous effects. The adrenals need not be removed by surgical means in order to prevent the leucocytosis. Since physostigmine (and strychnine) act upon the spinal cord to stimulate the glands, drugs which break the connection between cord and glands will functionally isolate the glands and thus prevent their stimulation with resulting leucocytosis. The functional removal of the glands is accomplished by ergotoxin, atropin and curare. Physostigmine given in small doses (0.5 mg. per kilo) to dogs causes no characteristic change in the number of red blood cells, while with slightly larger amounts (0.7 mg. per kilo) it markedly increases their number in the circulating blood. This increase seems to be due to an action upon the bone marrow, although changes in the concentration of the blood may play a part.

—I. B.

The effects of vitamin-deficient diets on the adrenal equilibrium in the body. Gross (L.), Biochem. J. (Lond.), 1923, 17, 569-578.

The Folin, Cannon and Denis method for adrenalin was used. Three hundred and fifty glands from 175 rats were studied. Pure vitamin deficiencies seem to set up very little alteration in the adrenalin equilibrium (relations between adrenalin store, gland weight and body weight) in the adult rat, providing the rat is not brought to the point of death. Such alterations as do occur can be explained on a basis of general tissue atrophy. In fact the adrenalin store in the adrenal gland maintains an extraordinarily constant proportion to the weight of the rat. It is suggested that this is no mere coincidence and that the way in which the store of adrenalin follows body weight in its changes caused by vitamin deficiencies is strong evidence for a finely controlled mechanism.—F. S. H.

The glycemic reaction after the subcutaneous administration of adrenalin (Beitrag zum Mechanismus der glykämischen Reaktion nach subcutaner Adrenalinzufuhr). György (P.) & Herzberg (E.), Biochem. Ztschr. (Berl.), 1923, 140, 401-409.

Children from  $\frac{1}{2}$  to 7 years old were used in these experiments. The results indicate that the reaction is composed of two phases, hyperglycemic and hypoglycemic. Previous treatment with bicarbonate, ultra-violet radiation or fever prevents hyperglycemia to a marked degree. The second phase dominates the picture. If the first phase is lacking entirely it is spoken of as the paradoxical inversion of the adrenalin blood sugar curve. Tetanic conditions are also accompanied by such a curve. This paradoxical situation may be associated with alkalosis or Ca-ion deficiency. The previous treatment with bicarbonate or ultra-violet radiation, and tetany often of themselves lead to hypoglycemia. Ammonium chloride increases hyperglycemia after adrenalin administration. It may produce the condition by itself. The acid-base equilibrium plays only a conditioning rôle in the reaction to adrenalin.—F. S. H.

The sensitiveness of the adrenal bodies to x-rays, and means to guard against injury to these bodies in deep x-ray therapy. Holfelder & Peiper, *Strahlentherapie* (Berl. u. Wien), 1923, 15, No. 1 (Jan. 17).

This investigation was begun at the Frankfort University Clinic upon the occasion of 2 subjects showing temporary symptoms of Addison's disease after irradiation of the upper abdomen. The authors review the interesting reports in the literature, which, however, are not altogether reliable on account of the lack of exact scientific procedure. Before giving their findings, so as to afford standards of comparison, they discuss at some length the normal microscopic anatomy of the adrenals in the guinea pig, the animals used for experimentation. The guinea pigs were bound to boards, with backs toward the tube, and were covered with leaded rubber, except one transverse strip 3 cm. wide in the region of the adrenals. The adrenals were determined to be at a depth of 1.5 to 2 cm. An H. S. H. tube, 42 cm. spark gap, 2 ma., 0.5 mm. zinc filter was used. In all but one animal the skin target distance was 30 cm. Various doses were applied to 15 animals. Some of the animals were killed after a time, and some died of extreme weakness. Autopsies and microscopic sections were studied. The authors give a detailed account of the pathological findings, and a number of microphotographs illustrating the changes which occurred.

The following conclusions were arrived at by the authors: The pathological changes in the radiated adrenals do not run parallel with the quantity of radiation. The clinical condition was not in agreement with the histological changes. One animal which received an 180% effectual dose and ran the worst clinical course gave absolutely normal histological findings. Another animal which received a 90% effectual dose died on the twenty-first day, and showed an extremely lipoid-poor adrenal body, which finding is often spoken of as adrenal scurvy. There were 3 subjects receiving 60%, 75%,

and 120%, respectively, which showed equally marked destructive changes. There were, on the other hand, subjects which received 60% and 100% with but slight changes. The conclusion is, therefore, that the sensitiveness of the adrenals to irradiation is markedly variable. This explains the variety of reports, in some of which small doses exerted marked influence, and in others large doses had no effect. Since in some persons the adrenals may have a particular sensitiveness to irradiation, the adrenal body should be excluded from the field of irradiation. Slight changes in the direction of the beam will be sufficient to avoid the adrenals.—*J. Radiol.*, 4, 375.

Alteration of the adrenals in experimental scurvy (*Über Nierenveränderungen beim experimentellen Skorbut*). Iwabuchi (T.), *Beitr. z. path. Anat. u. z. allg. Path.* (Jena), 1922, 70, 440.

In the form of experimental scurvy obtainable in guinea pigs by feeding with oats, typical and constant lesions of the adrenals are found. These consist in a marked diminution of the lipoids in the cells of the middle portion of the zona fasciculata and in an increase of the same materials in the cells of the zona reticularis of the cortex, double refracting substances having, on the contrary, almost completely disappeared. The cells of the zona fasciculata are, in addition, swollen, with pycnotic nuclei. Regenerative appearances in the shape of mitotically dividing cells are often found in the same areas. The capillaries, particularly of the zona reticularis and of the medulla, are extremely congested. The cells of the medulla have almost entirely lost their chromaffinity, and chromaffin material is no longer found in the blood vessels. The same cells are smaller and lighter than normal, while their nuclei stain very deeply. In merely starving guinea pigs the lipoids are greatly increased in all layers of the cortex, while double refracting substances are only somewhat diminished.—*Med. Sc.*, 8, 234.

The effect of suparenalectomy in the rat on agglutinin formation. Jaffe (H. L.) & Marine (D.), *Proc. Soc. Exper. Biol. & Med.* (N. Y.), 1923, 21, 64-66.

Animals were tested with injections of standard typhoid vaccine 8 and 13 days after operation. The adrenalectomized rats were more susceptible than the controls and showed a much higher antibody response. Rats, 30-50 days after operation, differed very little from normal animals in their reaction to injections of vaccine. The adrenal plays an important rôle in immunity. Rats rapidly compensate for the loss of their adrenals.—*J. C. D.*

The effect of adrenaline on left auricular pressure. McDowall (R. J. S.), *Quart. J. Exper. Physiol.* (Lond.), 1923, 13, 227-239.

The factors which affect the pressure changes in the left auricle when adrenalin is administered are the vagus, right ventricle,

The two phase activity of adrenalin (*Die zweiphasische Wirkung des Adrenalins*). Vollmer (H.), *Biochem. Ztschr. (Berl.)*, 1923, **140**, 410-419.

Studies of the phosphorus and calcium concentration of the blood of children and adults after the subcutaneous injection of adrenalin. The curves show a rise in calcium content, accompanied by a concomitant fall in phosphorus content. After this reaction has occurred, the concentration of these two elements returns to normal, and in the case of calcium falls below, while phosphorus rises above. These reactions occurred in the majority, but not all of the cases tested.—F. S. H.

The endocrines and epilepsy. Bassoe (P.), *Med. Clin. N. Am. (Phila.)*, 1923, **7**, 531.

A brief reference to the relationship of endocrine disturbance to epilepsy. The author concludes that there is nothing very convincing about any exclusive endocrine therapy to explain epileptic seizures.—I. B.

Drugs and basal metabolism. Boothby (W. M.) & Rowntree (L. G.), *J. Pharmacol. & Exper. Therap. (Balt.)*, 1923, **22**, 99-108.

Many of the more common drugs given in single moderate doses do not materially influence the basal metabolic rate. Iodin in the form of Lugol's solution nearly always causes a marked fall in the metabolic rate in patients with exophthalmic goitre. Adrenalin has a definite stimulating action on the metabolic rate with a maximum effect a few minutes after administration. Insulin, while not affecting the rate in the normal, causes an increase in conditions of hypoglycemia. Thyroxin possesses a definite calorogenic action which does not appear for several hours after administration and reaches a maximum effect only after several days.—G. E. B.

Glycerophosphatase in human organs (*Glycerophosphatase in menschlichen Organen*). Forrai (E.), *Biochem. Ztschr. (Berl.)*, 1923, **142**, 282-290.

Glycerophosphatase is an enzyme which splits up the phosphoric acid esters found in the body tissues. It was found that the thyroid, adrenals, testes, pancreas, thymus and spleen, among other organs, possess this enzyme. No organ of mesenchymal origin showed activity.—F. S. H.

Glands of internal secretion in experimental avian beri-beri. Kosenrenchevsky (V.), *J. Path. & Bacteriol. (Edinb.)*, 1923, **26**, 382. This investigation was carried out on 54 pigeons, all of which received a basal diet of polished rice and water, with various additions. Five groups were deprived of vitamin B, while the two remaining groups acted as controls. Beri-beri developed and the duct-

less glands of the animals thus affected were examined. The most characteristic changes were: (1) hypertrophy of the adrenals, (2) atrophy of the thymus, (3) atrophy of the spleen with persistence of the islets of the germ centers, often accompanied by an increase in their number and size and frequent hypertrophy of their cells. Some of the beri-beri pigeons showed other changes, but these were not regarded as characteristic. These consisted more particularly of a tendency to hypertrophy and hyperplasia of the interstitial cells of the testis and increase in number and hypertrophy of the large, pale cells of the hypophysis cerebri. In beri-beri-producing diets deficient in the fat-soluble factor, active changes occurred in the thyroid gland.—Med. Sc., 9, 102.

Achondroplasia and pseudo-achondroplasia (*L'achondroplasie et les cas pseudo-achondroplasiques*). Krabbe (K. H.), *Rev. neurol.* (Par.), 1923, 30, 127-139.

Of the various endocrine disturbances precocious puberty, above all, seems to be able to produce, through the early closure of the epiphysial lines, a shortening of the extremities which may give to the patient an aspect resembling somewhat that of achondroplasiac. The author believes, however, that there is no reason for supposing that true fetal achondroplasia is due to an endocrine disturbance.  
—C. E. N.

Gastric crises and sympathicotonia (*Crises gastriques et sympathicotonie*). Labbé (M.) & Sebileau (J.), *Bull. et mém. Soc. méd. d. Hôp. de Par.*, 1923, 47, 1224-1229.

The syndrome is attributed to irritation of the sympathetic ganglia due to sclerosis following pleurisy. The administration of adrenalin raised the blood pressure from 140/95 to 220/125, the pulse from 83 to 99; produced normal glycemia; and induced no hemoclastic shock.—F. S. H.

Diagnosis and indication for treatment of endocrinopathies by the Abderhalden reaction (*Diagnostico de las disendocrinias por la reacción de Abderhalden y en tratamiento específico*). Novaro (R.), Marco del Pont (A.) & Castaldo (F.), *An. d. Inst. mod. de clin. med.* (Buenos Aires), 1922, 7, 243.

Experiments were carried out on calves. Only pluriglandular disturbances were seen and complete classification is impossible. The Abderhalden test alone permits diagnosis of slight endocrine syndromes and indicates the proper therapy.—B. A. H.

Changes in the blood sugar content caused by internal asphyxia produced by blood poisons (*Ueber die Veränderung des Blutzuckergehaltes bei durch Blutgifte erzeugter innerer Asphyxie*). Tadenuma (K.), *Biochem. Ztschr.* (Berl.), 1923, 141, 86-96.

Hens and rabbits were used in this study. Blood poisons like phenylhydrazin and saponin produce noteworthy hyperglycemia only after the ingestion of food. The reaction is, therefore, not associated with mobilization of the liver glycogen. The glycogen forming ability of the liver is unaltered. The glycolytic power of the blood and the red cell count is lowered. Apparently there is a functional relationship between the two.—F. S. H.

Value of organotherapy (Experimentelle Untersuchungen über den Wert der Organotherapie). Zondek (B.), Ztschr. f. Geburtsh. u. Gynäk. (Stuttg.), 1923, 86, 238-277.

The most important conclusion drawn from these extensive experiments is that endocrine substitution therapy is possible only when desiccated preparations are used which are chemically unaltered; and by organ implantation. Organ extracts lose the specifically active substance during the process of preparation, particularly the deproteinization. The hypophysis is an exception. Extracts of different organs prepared in different ways were tested out on the frog heart, the surviving uterus, duodenum, and nerve-muscle preparation. Studies were also made of the blood form-elements and its coagulation time. A few observations were made on the respiratory exchange.—F. S. H.

Sex-reversal in the fowl. Crew (F. A. E.), Proc. Roy. Soc. (Lond.), 1923, 95B, 256-278.

A number of fowls are described which display conversion of an actively functioning hen into an actively functioning cock. This sex transformation is brought in line with the established principles of zygotic determination of sex in the fowl. There are successive invasions of the ovary by sex cords and the male characters are prevented by the presence of growing oocytes. In the absence of this inhibiting influence of the growing oocytes, spermatatic tissue is differentiated from the invading sex cords, and male characters develop —G. E. B.

The hormones of the placenta and corpus luteum and the lipiods of the latter [Ueber das Hormon (Geschlechtsstoff) der Placenta und des Corpus luteum, sowie die Lipoide des Corpus luteum]. Fränkel (S.) & Fonda (M.), Biochem. Ztschr. (Berl.), 1923, 141 379-393.

It is possible to extract from the corpus luteum a substance which to all appearances is the same as that obtained by Herrmann from the placenta. The compound is a viscous, light yellow body of turpentine odor. It has a boiling point of 194 degrees C., is insoluble in water but soluble in all organic solvents. The empirical formula is  $C_{22}H_{32}O_2$ .—F. S. H.

The placenta and the motor function of the uterus (Ueber Plazentastoffe und die motorische Funktion des uterus). Franz (T.), Monatschr. f. Geburtsh. u. Gynäk. (Berl.), 1923, 64, 7-30.

From experiments it is concluded that lipoids from any source can induce motor activity of the uterus simulating labor. Some amines act similarly. No amines are present in the fresh placenta which exert a stimulating action on uterine motility. Lipoids, however, are present.—F. S. H.

The influence of removal of sexual glands on the skeleton of animals kept on normal or rickets-producing diets. Korenchevsky (V.), J. Path. & Bacteriol. (Cambridge), 1923, 26, 207.

Negative results are reported.—R. G. H.

Experimental hermaphroditism. Krause (W.), Deutsche. med. Wchnschr. (Berl.), 1923, 49, 1330-1332.

Krause, working in Lipschütz's institute, confirms the possibility of producing artificial hermaphroditism by intratesticular implantations of ovarian substance. The action did not seem to depend on the amount of substance transplanted in the guinea pigs used.—J. Am. M. Ass.

Partial castration in white mice (Untersuchungen über Partialkastation an weissen Mäusen). Kropman (Esther), Skandin. Arch. f. Physiol. (Berl. u. Liepz.), 1923, 44, 76-78.

One entire testicle and greater or lesser amounts of the other were removed. The sexual characteristics were unaltered. Even when only small fragments remained, there was no hypertrophy of the interstitial cells and spermatogenesis took place.—G. E. B.

Rejuvenation experiments with vas ligation in rats. Macht (D. I.) & Teagarden (E. J.), J. Urol. (Balt.), 1923, 10, 407-413.

The author tested senile albino rats after ligation, using as controls animals on which a laparotomy was done without ligation. One group of animals was tested in a circular maze and another group on a tight rope. In the maze tests no difference between the groups could be noted. In the experimental group definite improvement in muscular co-ordination was shown by the ease with which the animals learned to walk a tight rope. This was associated with an improved appearance in the animals. These improvements were, however, transient, 6 weeks at most elapsing before the animals sank back into a senile condition like that of the controls.—J. C. D.

On the ovarian factor concerned in the occurrence of oestrus. Marshall (F. H. A.), J. Physiol. (Lond.), 1923, 58, 74-80.

Prooestrus and oestrus are due to a secretion from the follicles during the pre-inseminal stage of development. The corpus luteum



produces a secretion which is responsible for uterine and mammary hypertrophy during pregnancy, while normal nutrition is maintained by a third secretion from the smaller follicles or from the interstitial cells.—T. C. B.

**The internal secretions of the reproductive organs.** Marshall (F. H. A.), *Physiol. Rev. (Balt.)*, 1923, 3, 335.

This paper gives a critical account of the present state of our knowledge of the internal secretions of the reproductive organs. Comment is made on the fact that they differ from the internal secretions of other glands in being cylindrical. Recurrent changes occur in the female generative organs and are known as the oestrous cycle. The ovaries contain the controlling factor, for removal causes cessation of the phenomena, though transplantation of the removed ovary to another situation will prevent this. The assumption is that the ovaries exert their influence by an internal secretion. The possible elements which might produce this are: (1) the follicular epithelial cells; (2) the luteal cells of the discharged follicle, or (3) the interstitial cells. Evidence is adduced to show that it is unlikely that the corpus luteum exerts this influence. Possibly the mature follicles provide the internal secretion which is responsible for the phenomena, but in any case it seems evident from experimental observations that the ovarian hormones which produce oestrous are different from those which are responsible for maintaining the normal uterine nutrition. Considerable evidence is brought forward to show that the internal secretion of the corpus luteum sensitizes the uterine mucous membrane, thereby rendering it capable of reacting to mechanical stimulation. In pregnant animals in which the corpus luteum persists, the direct stimulus is produced by the fertilized ovum. Observations are recorded which indicate that the growth of the mammary glands is dependent on the stimulus derived from the corpus luteum. The author considers that there is no doubt that in the rabbit, marsupial, cat, and the bitch the corpus luteum is an essential factor in the growth of these glands. The commencement of milk secretion is marked by retrogressive changes in the corpus luteum. He also suggests that the katabolic changes concerned in actual milk secretion are probably influenced by the corpus luteum. Observations in polyoestrous animals on the corpus luteum are in conformity with these findings. It seems possible that during pregnancy, when the corpus luteum dominates the ovarian metabolism, the activity of normal ovarian secretion is reduced, but that at the end of pregnancy, when the corpus luteum involutes, ovarian secretion reasserts itself. The author mentions Dixon's recent work on the relation between ovarian and pituitary secretion. Dixon found that pituitary secretion was stimulated by ovarian extract, but not by extract of corpus luteum. The author suggests that when the corpus luteum involutes at the end of preg-

nancy the ovarian secretion may reassert itself and, by activating the pituitary, promote those uterine contractions which are the cause of parturition. It is not known what precise ovarian elements are responsible for the production of the hormone which excites the development of the female organs. There is an undoubted functional correlation between the ovaries and the normal nutritional condition of the uterus, for ovariectomy is followed by uterine degeneration which can be arrested by ovarian transplantation. The study of the distribution and comparative physiology of the ovarian interstitial tissue, however, is as yet imperfect; but it is suggested by Steinach that the interstitial cells of the gland are responsible for all essentially female characteristics. This observation is based on a large number of experiments. The growth of the accessory male organs and secondary male characteristics are dependent upon the presence of the testes. The assumption that this is due to an internal secretion is upheld by the effect of castration and the transplantation of testicular grafts into abnormal positions. The majority of evidence points to the fact that the internal secretion of the testicle is produced exclusively by the interstitial cells. All observations recorded point to the fact that the gonads play a very important rôle, if not the main one, in determining which sex is to develop. The interstitial cells are referred to by Steinach as "the puberty gland." His work on rejuvenation by vasectomy, or ligation of the vas deferens, is considered as well as Voronoff's claims. It is suggested that atrophy of the spermatogenetic tissue occurs without interfering with the interstitial tissue. Steinach goes farther and says that the interstitial tissue hypertrophies. The author considers that this is still an open question, but, in summing up, he suggests that there is no doubt that in mammals the internal secretion of the testicles is responsible for the development of the pubertal characteristics, while there is accumulating evidence that the presence of this gland in fetal life is very important in sexual differentiation before birth.

—Med. Sc., 9, 122.

**Hermaphroditism in man** (*Zur Kenntnis des Hermaphroditismus beim Menschen*). Matsuno (J.), *Arch f. Gynäk.* (Berl.), 1923, 119, 359-365.

Description of two hermaphrodites from whom the ovaries were removed and into whom others were implanted from healthy sources. In neither case was there any notable change in mind or body which could be attributed to the glandular implantation. Histological studies of the ovaries removed from the hermaphrodites showed no evidence of the presence of male elements. The observations are taken to indicate that the idea of an obligatory bisexual origin of the sex glands in hermaphroditism is unsustainable.—F. S. H.

**Testicle transplantation.** Report and demonstration of a case. McKenna (C. M.), *Illinois M. J.* (Oak Park), 1921, 40, 228-230.

The patient was a man of 26, who gave a history of having had both testicles removed because of tubercular infection. An undescended testicle of another patient was implanted. Improvement in health, strength, and sexual power was noted within a few days thereafter. This benefit was still evident at the time of the writing of this paper eight months later.—I. B.

On the general effects of exposure to radium on metabolism and tumor growth in the rats and the special effects on testis and pituitary. Mottram (J. C.) & Cramer (W.), *Quart. J. Exper. Physiol. (Lond.)*, 1923, 13, 209-226.

When small doses of radium radiation are applied over long periods to young male rats there results an increase in weight and marked obesity. There is also atrophy of the seminal tubules and hypertrophy of the interstitial cells, with changes in all three parts of the pituitary. From an analysis of these results it is concluded that the primary effect is atrophy of the seminiferous tubules, which gives room for hypertrophy of the interstitial cells. As obesity does not follow castration, it must be the result of the hypertrophy of the interstitial cells directly or indirectly. The hypertrophy also produces changes in the intermediate and posterior portions of the pituitary. The two components of the testis have different effects on the organism. Rats which have been exposed to radium are more resistant to the growth of transplantable tumors.—T. C. B.

Influence of testicular extracts on growth (*Acción de los extractos testiculares sobre el crecimiento*). Pillado Mathen (C.) & Damianovich (H.), *An. d. Inst. mod. de clin. med. (Buenos Aires)*, 1922, 7, 261.

Two experiments were performed on each of three chickens. Administration of autolytic testicle accelerated growth.—B. A. H.

What relation exists between the endocrine glands and sterility? Pottenger (F. M.), *Calif. State M. J. (San Fran.)*, 1923, 21, 465-466.

Any important organ may be in a state of dysfunction without evident structural changes. Sterility in women cannot be discussed on an anatomical basis only. The factors controlling impregnation are many and intimately related to the vegetative nervous system. Both normal structure and normal function of the sexual organs are essential to proper impregnation. This depends not only upon the ovaries, but also upon other endocrine organs, eminently the thyroid, pituitary, suprarenals and the thymus. Ovarian and thyroid hyposecretion, as well as pituitary hypo- and hyper-secretion, singly or in combination, may be responsible for sterility, calling for endocrine treatment. Finally, sterility may follow toxemia, especially from tuberculosis, typhoid fever and mumps.—I. B.

**The ovary in menstruation.** Ramírez (E.), *Gac. méd. de Mexico* (Mexico City), 1923, 55, 504-532.

Ramírez removed the corpora lutea in 3 patients during operations for displacement of the uterus, the fifth, ninth and seventeenth day after a menstrual period. Each of the women, three or five days after the operation, presented hemorrhage which seemed to be normal menstruation. The significance of the interstitial tissue of the ovary for the cyclic genital processes was studied in various animals, as he describes. These interstitial cells in the ovary are found not only in mammals, but also in birds, reptiles and other vertebrates. He argues that the interstitial gland is responsible for the secondary sexual characters, including rut and menstruation. It develops from the theca of the follicle after atresia, and the products of the interstitial gland have a widespread influence on various functions. This influence is manifest in the blood pressure during menstruation, as also in the different reaction to an extract of the menstrual secretion, applied to a scarified area, during or outside of a menstrual period. The fact that the premenstrual symptoms subside when the menstrual flow is under way, while they persist and become exaggerated if the menstrual flow is impeded or defective, suggests that these substances generated by the interstitial cells are eliminated in the menstrual flow.—*J. Am. M. Ass.*, 81, 1825.

**Experimental hermaphroditism.** Sand (K.), *Ugesk. f. Læger* (Copenhagen), 1923, 85, 565-574.

Sand has been conducting research in this line for years. He here describes the results in three series of guinea pigs, about 1 month, 3 months or 12 months old, in which gonads of the opposite sex had been transplanted. Ovaries transplanted into the testes showed that the sexual characteristics were still transversible, hormone-susceptible, even when puberty was well advanced, as well as in the younger animals. But the experiments always failed in the adult animal. The mammae in the male can enlarge and secrete milk merely under the influence of an ovary implanted in the testes. The bisexual characters at first gradually changed so that one or the other sex finally predominated. This field of experimental hermaphroditism has demonstrated that even the microscope is too coarse an instrument to explain all the facts observed.

—*J. Am. M. Ass.*, 81, 1830.

**The mental state of eunuchoids (*L'état des eunuchoides*).** Sterling (W.), *Rev. neurol. (Par.)*, 1923, 30, 492-499.

A discussion of the psychic status of eunuchoids. Three components may be present in their mental disturbances: (1) epileptic; (2) oligophrenic; and (3) disdiastematic (from the name of "la glande diastématique" or interstitial). In each case of eunuchoidism at least one of these components is present.—*C. E. N.*

Experimental attempt at increasing the growth of the uterus (*Experimentelle Versuche das Wachstum des Uterus zu steigern*). Zondek (B.), *Arch. f. Gynäk.* (Berl.), 1923, 120, 251-255.

Zondek believes that growth of the uterus depends on ovarian function. Using guinea pigs as experimental animals, he was able to demonstrate a growth-promoting effect on the uterus of extract of the ovary and testes. Thyroid and corpus luteum were ineffective.—F. S. H.

Diet treatment of diabetes insipidus. Allen (F. M.) & Sherrill (J. N.), *J. Metab. Res.* (Morristown), 1923, 3, 479-510.

A report of 4 cases of diabetes insipidus in which an etiological therapeutic study was made. The object of the experiments was to determine the effect of a restriction of various elements in the diet on the thirst and polyuria of this disease. The intake of water, salt, nitrogen, fat and carbohydrate were studied. The effect of pituitary extract was also observed. It was noted that plasma chloride was slightly above normal in 2 cases, although it was low in a third. The red cell volume was high in all subjects examined, although the hemoglobin and red cell counts were comparatively low. Pituitary administered intranasally or subcutaneously was found to reduce the thirst and polyuria, at the same time raising the concentration of the urine. As pituitary is known to reduce the urine similarly in normal persons, the authors could not feel sure that its action in these cases of diabetes insipidus represented a true hormonal substitution. Radical restrictions of protein and salt caused a reduction in the thirst and polyuria, whereas, heavy protein feeding caused an increase in these symptoms with a flushing out of chlorides. Restriction of sodium chloride was essential in the treatment of all cases studied, apparently being more potent than nitrogen restriction. The best results were obtained when the sodium chloride was so restricted that less than a gram appeared in the 24-hour urine specimen. No untoward effect was observed to follow this restriction. The authors conclude that the essential disorder in diabetes insipidus does not consist in loss of concentrating power on the part of the kidneys.—I. M.

Hypophyseal extracts in obstetrics (*La question des injections d'extraits hypophysaires dans la pratique obstétricale*). Chatillon (F.), *Rev. franç. de gynéc. et d'obst.* (Par.), 1923, 13, 448-453.

From a consideration of recent evidence Chatillon reaches the conclusion that hypophyseal extracts injected hypodermically or intramuscularly constitute the best oxytocic known at the present time and that they are not dangerous when used strictly according to rule. Injections should be made only during the period of expulsion or toward the end of the period of dilation, when the head is normally engaged. Thus delivery is hastened by diminishing the

duration of the period of expulsion. During delivery hypophyseal extracts do not seem so effective as preparations of ergot. On the contrary, pituitrin introduced intravenously manifests a much more pronounced action on the uterus than ergot preparations.—R. G. H.

The significance of an achondroplasia-like condition met with in cattle. Crew (F. A. E.), Proc. Roy. Soc. (Lond.), 1923, 95B, 228-255.

Dexter cattle were studied as to the cause of the frequent occurrence of still-born calves presenting certain constant abnormalities resembling the condition of achondroplasia met with in the human being. The activity of the posterior lobe of the "bull-dog" fetus was tested by the melanophore reaction and found to be much less active than that of the normal fetus of the same age. From this it was inferred that the anterior lobe is also hypofunctioning. The thyroid, after development, undergoes a hyperplasia followed by retrogression and colloid formation in the older specimens. This condition is not believed to add support to the theory that the condition is that of cretinism. The adrenals were never found to be perfectly normal. The authors believe that possibly the condition results from malfunction of the pituitary between the second and third month of intrauterine life.—G. E. B.

Cutaneous and genital alterations in the toad in lesions of the hypophysis (*Alteraciones cutáneas y genitales en el sapo por lesiones de la hipófisis*). Giusti (L.) & Houssay (B. A.), Rev. Asoc. méd. argent. (Buenos Aires), 1923, 36, 77.

Hypophysectomized toads survive in large numbers for 3 months; they become black, due to the formation of a cuticle—which is also seen in the denervated foot. The phenomenon is not modified by organotherapy. Lesions of the infundibulum (in 100% of the cases), of the optic lobes (50%) and of the thalamus (25%) produce a blackness which is not obtained by lesions of other regions. There is usually abortion within 48 hours in females in whom the infundibulum is injured or the hypophysis removed.—B. A. H.

Case of Frölich's syndrome following injury to the sella turcica. Hendry (J.), Glasgow M. J., 1921, 96, 147-150.

The case reported is that of a married woman of 26 whose history of 3 months' amenorrhea, subcutaneous tissue thickening, mental dullness, and cold limbs led to a tentative diagnosis of subthyroidism. Thyroid opotherapy, however, failed to control the progressive increase in weight, drowsiness, and apathy. A few weeks before the onset of amenorrhea the patient had slipped on the sidewalk and fallen backwards, striking her head. She was at first dazed; later there was a complete loss of vision, which subsequently returned. This led to a suspicion of a pituitary lesion.

The administration of 1 gm. of whole pituitary gland resulted in no relief. Within the following year the patient presented the complete picture of Frölich's syndrome. X-ray examination revealed a fracture of the base of the skull, involving the sella turcica. At this time hypodermic injections of extract of anterior pituitary resulted in marked subjective and objective improvement.—I. B.

**Influence of infundibulo-hypothalamic lesions on growth** (*Influencia de las lesiones infundíbulo-hipotalámicas sobre el crecimiento*). Houssay (B. A.) & Hug (E.), *Rev. Asoc. méd. argent. (Buenos Aires)*, 1923, 36, 11; see also, *Compt. rend. Soc. de biol. (Par.)*, 1923, 80, 51-53.

Experiments were carried out on 3 families of young dogs. In spite of severe lesions of the hypothalamic region and of the tuber, growth was normal. In one instance there was atrophy of the testicle.—B. A. H.

**Traumatic lesions of the hypophysis** (*Contribution à l'étude des lésions traumatiques de l'hypophyse; volumineux kyste hémorragique de cette glande, consécutif à une contusion du crâne*). Reverchon (L.), Delater (G.) & Worms (G.), *Rev. neurol. (Par.)*, 1923, 30, 217-225.

One year after a violent contusion of the head the patient was found to have bitemporal hemianopsia; about 2 years after the injury diminution of sexual desire and ability set in; there were physical changes indicative of hypopituitarism, which became marked in the following 3 years. Polyuria and glycosuria also developed. The skiagram showed an enlargement of the sella turcica. With x-ray therapy there was some regression of symptoms. The patient died after a transphenoidal operation on the pituitary. At autopsy a tumor anterior to the peduncles was enucleated from the fossa which represented the sella turcica. The authors believe that the original lesion was a hemorrhage in the anterior lobe, which was quiescent for a long time and then, little by little, became encysted. This observation proves that an alteration of the pituitary great enough to correspond to nearly complete disappearance of the gland is compatible with life for a period of time. The adiposo-genital syndrome and the diabetic symptoms cannot be attributed to the pituitary, as the infundibulum was involved.—C. E. N.

**The weight of the hypophysis of the horse** (*Untersuchungen über die Hypophysengewichte von Pferden*). Saito (Y.), *Biochem. Ztschr. (Berl.)*, 1923, 142, 308-311.

A study of the absolute and relative weight of the hypophysis of many horses during the different months of the year. It was found that the weight of this gland in mares was greater in the months of June and July than at other times; that the gland was

heavier in pregnant mares than in non-pregnant animals, and that in horses the weight was less than that of the mares. The differences in weight are due to the anterior lobe. Some 372 animals were used for the study, of which 14 were horses (castrates) and 6 pregnant mares.—F. S. H.

Pituitary extract (*Sobre extracto hipofisario*). Turenne (A.), *An. de la fac. de med. (Montevideo)*, 1923, 8, 625-630.

Turenne publishes an open letter in reply to the question-blank sent out by de Cotret of Montreal. Turenne says that the present tendency to abuse of pituitary extract is certain to discredit this extremely valuable drug. He reiterates that the indications for its use are moderate inertia of the uterus, when there is no mechanical obstacle to delivery, and there is no reason to suspect weakness or excessive fatigue of the uterine muscle. Heart and kidney diseases, goiter, pregnancy toxemia and emphysema are further contraindications. He has had one fatal case in his service, although all the indications and contraindications had been scrupulously observed, and several women have died of those brought in after pituitary had been given outside the hospital. Months pass in the maternity in his charge without pituitary extract being considered necessary. "No drug has yet been discovered that has an action physiologically identical with that of the normal mechanism of delivery."

—J. Am. M. Ass., 82, 68.

The influence of hypophysectomy on the rate of carbon-dioxide production frogs. Winton (F. R.) & Hogben (L. T.), *Quart. J. Exper. Physiol. (Lond.)*, 1923, 13, 309-322.

Removal of the pituitary results in a lowered carbon dioxide production in frogs, and preliminary experiments indicate the same is true when the anterior lobe alone is removed.—T. C. B.

Food mixtures suitable for diabetic patients receiving insulin and a method for calculating diets. Adams (S. F.), *Med. Clin. N. Am. (Phila.)*, 1923, 7, 13-24.

A valuable paper on the dietary phase of the management of diabetes mellitus. If insulin is to be used with the success it deserves, the patient's diet must receive most careful attention. While drastic restrictions in diet are open to criticism, a proper limitation of food is important. The relationship of the diet to the basal metabolism is discussed. The author believes that not the acidosis *per se*, but rather the dietary conditions giving rise to acidosis, result in an increased basal metabolism. In feeding protein the nitrogen balance must be constantly borne in mind. Carbohydrates should be given only in such amounts as are sufficient safely to balance the ketogenic effect of the fatty acids. The balancing of the ketogenic (fatty acid) and the antiketogenic (glucose) materials in



a food mixture is of primary importance, since upon this depends the degree of liability to acidosis. A modification of a dietary chart proposed by Wilder, to serve as a guide to a low maintenance diet which may be used in conjunction with insulin treatment, is described in detail. This chart has the advantage of being a simple and accurate means of determining the amount of fat, protein and carbohydrates of an aketogenic diet, its total calories, and sugar value, when any two of these five variables are known and fixed.

—I. B.

**The influence of fat and total calories on diabetes and the insulin requirement.** Allen (F. M.), *J. Metab. Res.* (Morristown), 1923, 3, 61-176.

An attempt was made to determine the relationship between the insulin requirement and the various factors in the diet, special emphasis being laid upon the relationship of insulin to fat utilization in diabetic subjects. The author gives a very extensive review of the different types of diet used in the treatment of diabetes in this country, pointing out the advantages of under-nutrition in the early treatment of disease as opposed to attempts at increasing the weight by inclusion of large amounts of fat in the diet. He presents much evidence in favor of his own views from a new angle. The latter study has been made possible by the discovery of insulin. The author concludes that the insulin requirement is governed, not alone by the carbohydrate in the diet, but by the other substances present, including the fat, although it remains uncertain whether insulin is concerned in the total metabolism. He believes that it probably is concerned, although the evidence is inconclusive. He found that the minimum insulin requirement compatible with glycosuria may be roughly estimated in severely diabetic animals and patients. This minimum requirement was found to be as low as 4 units per day in young children and 12 units or more for an adult, although more than twice this amount is assumed to be required for maintenance of life even on the lowest plane of nutrition. He concludes that the need for insulin is quantitatively related to the body mass as well as to the amount of food to be metabolized. The insulin requirement of children is lower absolutely, but higher per kilogram of body weight, than that of adults. The author believes that increase in adipose tissue requires a greater amount of insulin than an increase in active protoplasm, and that this need occurs, not only during the building up of this new tissue, but continues undiminished as long as the extra tissue is kept. This, the author believes, explains the diabetogenic influence of *luxus* diets and obesity, as previously observed. The final conclusion is that under-nutrition of a certain degree should be maintained in conjunction with insulin therapy to obtain the best results.—I. M.

The relation of the adrenals to diabetes. Allen (F. M.), *J. Metab. Res.* (Morristown), 1923, 3, 589-621.

The investigation was undertaken in 1917 and 1918 to determine the possible relationship of the adrenal function to diabetes. Three lines of investigation were followed, namely, partial epinephrectomy, fat feeding in connection with epinephrin injections and epinephrin injections in partially depancreatized dogs. It was found that removal of most of the adrenal tissue of the dog does not disturb carbohydrate tolerance as judged by intravenous injections of glucose, and that the tendency to diabetes was unaffected by this procedure. Epinephrin glycosuria was not increased by forced fat feeding, a fact which shows epinephrin glycosuria to be unlike diabetic glycosuria. When epinephrin was injected at daily intervals over a considerable period of time in partially depancreatized dogs with latent diabetes, no increased tendency to active diabetes was observed. The glycosuria under such circumstances was only slightly greater than that produced in normal animals by the epinephrin injections. The glucose appeared to rise in all cases from breakdown of glycogen and not from destruction of protein. In these animals with latent diabetes epinephrin apparently failed to produce the vacuolation of the remaining islet cells of the pancreas, which occurs with any functional strain. These facts indicated that epinephrin is not a diabetogenic agent or a physiological antagonist of insulin. Epinephrin injections were found to cause a much greater elimination of nitrogen and sugar in an animal with active diabetes than in normal animals or animals with latent diabetes. In active diabetes extra destruction of protein was observed to be a feature.—I. M.

Diabetes and phlorizin glycosuria. Allen (F. M.), *J. Metab. Res.* (Morristown), 1923, 3, 623-639.

The possible relationship of phlorizin glycosuria to diabetes mellitus was studied in connection with three questions: (1) the special lability of diabetic tissues; (2) the influence of phlorizin glycosuria upon diabetes; and (3) the comparative effects of phlorizin glycosuria and diabetes. The method employed for studying the first question was that of determining the effects of phlorizin poisoning upon dogs with mild and severe diabetes previously under complete control by diet or fasting. The urinary sugar and nitrogen were determined as indices of the amount of protein destruction. When compared with normal dogs subjected to the same treatment, no difference was found. When the phlorizin was given to animals in which the diabetes was active, a great amount of sugar and nitrogen was excreted, showing that in these animals the phlorizin causes acceleration of protein breakdown. This the author interprets as being due to deficiency of insulin in the case of active diabetes, and not as abnormal tissue lability. To determine the influence of

phlorizin glycosuria on diabetes, phlorizin was given to diabetic animals. Doses were employed which caused continuous glycosuria with hypoglycemia and loss of weight. It was found that diabetic animals given a diet in excess of their tolerance showed no impairment of the tolerance while taking phlorizin. The loss of weight caused by the phlorizin was found to raise the tolerance like ordinary under-nutrition. It was found also that phlorizin does not injure the islets of Langerhans. The effects of diabetes and phlorizin glycosuria on animals was determined under as nearly similar conditions as possible. Fasting dogs receiving phlorizin in sufficient doses to produce excretion of sugar and nitrogen in amounts corresponding to those excreted by totally depancreatized dogs showed far less impairment of their healing and resisting power and far less asthenia than the latter. The partially depancreatized dogs on a given diet were found to weaken and die with active diabetes, while phlorizinized control, receiving the same diet and excreting a similar quantity of sugar and nitrogen, survived. Phlorizin when administered did not save such diabetic animals. The conclusion is drawn that phlorizin poison is radically different from diabetes and that diabetic symptoms and death are not explainable wholly by the loss of sugar.—I. M.

**Oxidation of glucose by iodine in the presence of insulin.** Alles (G. A.) & Winegarden (H. M.), *J. Biol. Chem. (Balt.)*, 1923, 58, 224-234.

Strictly comparable experiments were made with glucose alone, with mixtures of it with insulin, with insulin and liver extract, or with insulin and blood serum or oxalated blood, in order to determine whether the substance affects oxidation of glucose by iodine. In no case was any difference detected in the rate of the reaction. This shows that no appreciable reaction takes place between glucose and insulin even in the presence of the animal products mentioned. It indicates, therefore, that the metabolic processes must be more complicated in character; also, that there is little promise of developing a method of assay for insulin on the basis of its action on glucose.—F. S. H.

**An insulin-like substance in the kidney, spleen and skeletal muscle.** Ashby (J. S.), *Am. J. Physiol. (Balt.)*, 1923, 67, 77-82.

A substance can be extracted from the kidney, the spleen and the muscle of normal dogs which will reduce the blood sugar of rabbits. It can be demonstrated only after the removal of the "toxic fraction," which has a hyperglycemic effect.—T. C. B.

**Possible sources of insulin.** Best (C. H.) & Scott (D. A.), *J. Metab. Res. (Morristown)*, 1923, 3, 177-179.

A very brief report of experiments in which a substance resembling insulin was obtained from various forms of vegetable matter.

A relatively large amount of the material was finely minced and extracted with acid alcohol and concentrated in vacuo. This concentrated filtrate was then injected into fasting rabbits. Blood sugar specimens were obtained before and from 1 to 6 hours after the injection. It was found that an insulin-like substance was present in potatoes, rice, wheat, beet roots and celery. The authors do not claim that this substance is identical with insulin, although further work is being done to determine more definitely its nature—I. M.

**Glucokinin.** An apparent synthesis in the normal animal of a hypoglycemia-producing principle. An animal passage of the principle. Third Paper. Collip (J. B.), J. Biol. Chem. (Balt.), 1923, 58, 162-207.

Profound hypoglycemia has been observed to occur in normal rabbits injected with certain plant extracts, extreme overdosage of insulin, with injections of guanidine sulfate, after prolonged fasting and spontaneously. The last is associated with the finding of *Coccidia oviforme* in the liver. The blood of normal rabbits which have developed hypoglycemia under any one of the above circumstances has produced profound hypoglycemia when injected into other normal rabbits. Animal passage (rabbit) of a hypoglycemia-producing principle seems to be possible to an indefinite extent. The symptoms are weakness, which may lead to collapse, convulsions and death. The symptoms of extreme weakness or convulsions have been relieved by the administration of glucose. The symptoms continue to reoccur at intervals of a few hours. They are in most cases effectively relieved by glucose for a time, but death eventually resulted. The following observations have been made with regard to the nature of the principle: (a) it is active after autoclaving at 15 pounds; (b) it can be dialyzed; (c) watery solutions can be concentrated by boiling over a free flame; (d) it is present in the filtrate obtained after treating passage blood with tungstic acid (Folin-Wu technic); and (e) it can be removed from passage blood by ammonium sulfate. A lethal dose for a full grown rabbit may be contained in as small amount of passage blood as 0.05 cc.

—F. S. H.

The free sugar content of the liver and its relation to glycogen synthesis and glycogenolysis. Cori (C. F.), Cori (G. T.) & Poucher (G. W.), J. Pharmacol. & Exper. Therap. (Balt.), 1923, 21, 377-389.

Using rabbits and guinea pigs, the authors found that during the ingestion of glucose, glycogensynthesis takes place from a free sugar level above that of the starving animal. Iletin causes glycogen to be formed during the ingestion of glucose, even though the blood sugar and free liver sugar may be below that of a starved animal. Adrenalin stimulates glycogenolysis at once, reaching a maximum in 30-60 minutes. This sugar gets into the blood stream slowly

and the highest blood sugar is at a point where the free liver sugar has begun to decline.—G. E. B.

A study of the rabbit as a test animal for determining the potency of insulin preparations. Clough (H. D.), Allen (R. S.) & Root (E. W. Jr.), *Am. J. Physiol. (Balt.)*, 1923, 66, 461-484.

The rabbits should be absolutely normal, free from the effects of previous injections, with a normal blood sugar level of 0.113, within a deviation of 0.017. Dosage should be proportional to the weight of the rabbit, and should produce a fall of not more than 0.070 gm. A Rochester "rabbit unit" is an absolute drop of 0.070 gm. in 2 hours in a rabbit weighing 2 kilos.—T. C. B.

Comparative study of the blood sugar concentration in the arterial and venous blood of diabetic patients during insulin action. Cori (C. F.), Poucher (G. W.) & Bowen (B. D.), *Proc. Soc. Exper. Biol. & Med. (N. Y.)*, 1923, 21, 122-123.

The authors used a new method for obtaining blood from the hepatic vein. In animals they found that the fall in blood sugar following the injection of insulin was due to a decreased sugar output from the liver and an increased absorption of sugar from the blood by the muscles. Observations on diabetic patients indicate similar increased absorption by the muscles.—J. C. D.

The effect of insulin treatment on the hydrogen ion concentration and alkali reserve of the blood in diabetic acidosis. Cullen (G. E.) & Jonas (L.), *J. Biol. Chem. (Balt.)*, 1923, 57, 541-552.

The acidosis of severe diabetes is characterized by the lowering of both alkali reserve and plasma pH. Under insulin treatment both alkali reserve and pH return to their normal level coincidentally. There appears to be a consistent relation between these two factors during the return to normal. Two cases of coma with recovery under insulin treatment with plasma pH at 38° of 6.98 and 7.02 respectively are reported. These are believed to be the lowest values for human plasma pH with recovery that have been reported.

—F. S. H.

I. Preparation of insulin. II. The absorption of insulin from the intestines, vagina and scrotal sac. Fisher (N. F.), *Am. J. Physiol. (Balt.)*, 1923, 67, 57-64; 65-71. III. Excretion of insulin by the kidneys. Fisher (N. F.) & Noble (B. E.), *ibid.*, 72-76.

I. There are two antagonistic substances in the pancreas: one, a "toxic fraction," causes death with a rise in blood sugar; the other, "active fraction," is the specific antidiabetic substance, insulin. The yield of insulin per kilo of pancreas is proportional to the degree of removal of the toxic substance. The toxic fraction causes irritation and sterile abscesses.

II. Injections into the scrotal sac yield the best results per unit of insulin. The temporary action when insulin is introduced into the gut is due in part to rapid elimination by the kidneys, suggesting too rapid absorption. Insulin is absorbed by the vagina and produces a temporary lowering of blood sugar.

III. Insulin can be recovered from urine in amounts varying with the rate at which it enters the blood stream. It is more marked when given by mouth, vagina or scrotal sac than when given subcutaneously.—T. C. B.

The treatment of diabetic coma with insulin. Foster (N. B.), Tr. Ass. Am. Physicians (Phila.), 1923, 38, 382-393.

A report of 15 cases of diabetic coma treated with insulin. Eight patients recovered and of these 5 are still alive. It is emphasized that acidosis, desiccation of the tissues and myocardial weakness are especially notable in diabetic coma. The method of administration of insulin and the question of giving fluids and alkalies are discussed.—I. B.

Blood sugar levels in diabetes when first seen. Gray (H.), Med. Clin. N. Am. (Phila.), 1923, 7, 675-685.

This report is based on observations upon 2000 consecutive diabetics seen in the New England Deaconess Hospital since Dec. 10, 1914. The following conclusions are drawn: (1) if diabetes is fairly certain, then the taking of post-absorptive blood sugar (before breakfast, or as long after the preceding meal as can be arranged) is advocated; (2) conversely, if renal or mild glycosuria seems possible from lack of symptoms and from less than 1% of sugar in the urine, then the blood sugar value after meals is more desirable than that before. One should avoid blood sugar determinations at random times.—I. B.

Diabetic coma and its treatment. Joslin (E. P.), Med. Clin. N. Am. (Phila.), 1923, 7, 637-640.

With existing methods of treatment diabetic coma need not occur even in intercurrent infections. The physician should (1) confirm the diagnosis, (2) give insulin at once, (3) protect the heart with hypodermic injections of digitalis and caffeine, (4) give salt solution subcutaneously to assist elimination and circulation, (5) wash out the stomach if deemed feasible, (6) continue the treatment of the disease, diabetes, and not the symptom, coma. Insulin should be given to protect the patient and not glucose to protect the insulin. The administration of alkalis is likewise unnecessary.

—I. B.

The feeding of odd carbon fatty acid fats to diabetic patients. Kahn (M.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1923, 21, 31-32.

Glyceryl ester of margaric acid is converted into glucose in dogs as shown by the author's experiments. In diabetic patients clinical evidences show that it is well tolerated and can be added to the diet to obtain as much as 1000 calories a day.—J. C. D.

Personal experiences with the use of iletin (insulin) in the treatment of diabetes mellitus. Lichty (J. A.), *Atlantic M. J. (Harrisb.)*, 1923, **27**, 5-11.

Experiences with insulin in 27 patients are reported. The adult with transient glycosuria and the nephritic with glycosuria need no iletin treatment. In true diabetics treatment is necessary only in those who continue to have glycosuria or who have a blood sugar above 0.15 to 0.17 on a diet furnishing less than approximately 30 calories per kilo. Children, however, may require continuous insulin treatment to maintain health and efficiency. In Lichty's experience the patient's carbohydrate tolerance may be elevated by iletin in a way never before experienced. Not only is this substance of great value in diabetic coma, but the horror of diabetic gangrene is now a thing of the past. We cannot as yet state whether ultimate cure can be expected in certain cases, and how long the treatment must be or can be safely carried on.—I. B.

Are the livers of frogs which have been rendered diabetic through pancreas extirpation sensitive to adrenalin (Sind pankreasdiabetische Lebern adrenalinempfindlich)? Lesser (E. J.) & Zipf (K.), *Biochem. Ztschr. (Berl.)*, 1923, **140**, 434-438.

It was shown that the extirpated liver of the frog rendered diabetic through pancreas removal formed six times as much sugar when perfused with physiological salt solution as did livers from normal animals. Adrenalin did not increase this sugar-forming ability in the test liver more than it did in the normal. It is concluded that there is present in the liver from the diabetic animals dissolved but not adsorbed diastase. From this premise it is further concluded that insulin makes possible the absorption of diastase in the liver. Therefore it should be possible to retard the disruption of this adsorption caused by surface active bodies by insulin.

—F. S. H.

The effect of fasting in diabetes as compared with a diet designed to replace the food-stuffs oxidized during a fast. Richardson (H. B.) & Mason (E. H.), *J. Biol. Chem. (Balt.)*, 1923, **57**, 587-611.

By means of a respiration calorimeter the amounts of protein, fat and carbohydrate oxidized by diabetic patients at rest were determined. The same amounts were then given in the diet, which was called the replacement diet. With this the metabolism was held at the level previously held in fasting. The replacement diet was

attended with an increase in the amount of protein and carbohydrate oxidized and of glucose excreted. To remedy this defect it should be modified by decreasing the protein and carbohydrate and increasing the fat, thus approaching the Newburgh type of diet. A method is described for the quantitative comparison of the food ingested with the food oxidized. Diabetic patients receiving their basal caloric requirements plus, in several instances, considerable quantities of fat oxidized more protein, more carbohydrate, and less fat than they received. In other words, to their allowance of food they added protein and carbohydrate derived from their own tissues, and subtracted a considerable portion of the fat for storage. It is inferred that the quantities of food eaten by diabetic patients may be widely different from the quantities oxidized, and that calculations based on the diet are subject to error. The above results apply strictly only to diabetic patients at rest.—F. S. H.

Does insulin influence the glycogenic function of the perfused liver of the turtle? Noble (E. C.) & Macleod (J. J. R.), *J. Physiol.* (Lond.), 1923, 58, 33-40.

Adding insulin to the perfusion fluid has little if any effect on the glycogen of the turtle's liver.—T. C. B.

Two cases of diabetic coma. Root (H. F.), *Med. Clin. N. Am.* (Phila.), 1923, 7, 641-645.

A report of recovery with insulin treatment in a male aged 15 and a female aged 28. Caution in the giving of fluids by mouth is important, as resulting stomach dilatation and cardiac embarrassment hinder recovery.—I. B.

The influence of carbohydrate and protein on diabetes and the insulin requirement. Sherrill (J. W.), *J. Metab. Res.* (Morristown), 1923, 3, 13-59.

The purpose of the work reported in this paper was that of determining the changes in insulin requirement in diabetic patients made necessary by additions, withdrawals and substitutions of carbohydrates and proteins in the diet. The author first adjusted the diet to the insulin dosage in patients, and then studied the effects on the blood sugar and urinary sugar of changes in the amounts of carbohydrate or protein in the diet. A large group of cases was examined. It was found that carbohydrate requires a greater amount of insulin than its caloric equivalent of protein to prevent glycosuria or hyperglycemia. Though hypoglycemia was prevented by sufficiently large quantities of protein, this influence proved surprisingly feeble and far below the theoretical glucose value of protein. No constant relationship between the number of grams of glucose and the units of insulin was found to exist, either in different individuals or in the same individual under these conditions. Gly-



cosuria and insulin requirement were found to be governed to a very important degree by the total caloric value of the diet.—I. M.

**On the action of insulin after extirpation of the adrenals** (*Sur l'action de l'insulin après l'extirpation des capsules surrénales*). Sundberg (C. G.), *Compt. rend. Soc. de biol. (Par.)*, 1923, 89, 807-810.

The administration of insulin reduces the blood sugar, while adrenalin increases it. Rabbits with the adrenals totally removed and those with the adrenal cortex grafted into the epiploön after total removal are more sensitive to insulin than the controls.

—T. C. B.

**Experimental pancreatic diabetes** (*Diabète pancréatique expérimental, ablation totale du pancréas en un temps sans ligature, par simple énucléation. Modifications qu'apporte à l'évolution du diabète ainsi créé l'emploi de l'insuline*). Thiroloix (J.), *Bull. et mém. Soc. méd. d. hôp. de Par.*, 1923, 47, 1352-1356.

When the administration of insulin accompanied the ablation of the pancreas in dogs two types of diabetes arose. When the procedure was as given in the title a "fixed" diabetes of sudden onset, accompanied by continuous and marked glucosuria, was produced; this was but slightly modifiable even by large doses of insulin. On the other hand, after section of the pancreas with ligature and remnants of glandular debris, a "variable" diabetes followed. There was delayed onset, and intermittent glucosuria, which was modifiable by insulin. This seems to be a substance of excito-secretory nature which stimulates the residual islets, and once the excitation is produced the secretion of the previously inert cells is prolonged for some time. In completely depancreatized dogs, large doses of insulin have but a slight and transitory effect.—F. S. H.

**Renal function in diabetes** (*Les fonctions rénales des diabétiques*). Urech (E.), *Ann. de méd. (Par.)*, 1923, 14, 231-248.

A study of the renal function of 12 diabetics. It was found that in 4 young patients there was no disturbance of chloride or urea excretion. It appears that in cases of this type the kidney cells, although unable to prevent the excretion of sugar, have kept intact their other functions. All older patients, however, seem to show a varying degree of disturbance of renal function. The ability to concentrate the urine is frequently diminished, chloride retention is marked, particularly when the patient is over 55 years of age, and the blood urea is always highly variable. It is concluded that neither the severity of the diabetes, the degree of the glycemia, nor the presence or absence of acetone exert a dominant influence upon the renal functions of diabetics, but that the vascular conditions, the arterio- or renal-sclerosis are responsible.—F. S. H.

Insulin. Wilder (R. M.), *Med. Clin. N. Am. (Phila.)*, 1923, 7, 1-12.

A general review of the researches on the pathogenesis and treatment of diabetes mellitus, with remarks on the use of insulin, based upon observations on 150 patients at the Mayo Clinic. Despite its remarkable life-saving properties in diabetic coma, and in diabetics with gangrene, pneumonia, and other general and local infections, insulin is by no means necessary in every case of diabetes mellitus. Insulin is not an essential adjunct in the treatment of the types of diabetics met with in obese and arteriosclerotic patients. Its efficacy in mild, chronic cases is also still open to question. Insulin is not a cure; it insures an increase of carbohydrate tolerance while it is being used. Insulin dosage must be carefully balanced with the food intake. The patient must be taught to understand and carry out the necessary dietary regulations, the use of insulin, and the emergencies which may arise. This can be accomplished only through a systematic course of study.—I. B.

Observations on the solubility of insulin. Widmark (E. M. P.), *Biochem. J. (Lond.)*, 1923, 17, 668-670.

Insulin is insoluble or very slightly soluble in tetrachlormethane, ethyl acetate, ethyl alcohol, isobutyl alcohol, amyl alcohol, chloroform, acetone, light petroleum, ethyl ether, benzine, xylene and pyridine. It is easily soluble in methyl alcohol, glacial acetic acid, phenol and formamide. Several facts point to the possibility of its being an albumose.—F. S. H.

On the absorption of insulin from the stomach. Winter (L. B.), *J. Physiol. (Lond.)*, 1923, 58, 18-21.

Insulin in weak alcoholic solution administered by mouth to rabbits caused a marked fall in blood sugar. This was not the case when the insulin was dissolved in N/20 NaOH.—T. C. B.

On a possible relation between the pancreas and the parathyroids. Winter (L. B.) & Smith (W.), *J. Physiol. (Lond.)*, 1923, 58, 108-109.

After a preliminary injection of parathyroid extract into rabbits, convulsions follow a dose of insulin one-third to one-quarter of the normal dose.—T. C. B.

The action of proteolytic enzymes upon insulin. Witzemann (E. J.) & Livshis (L.), *J. Biol. Chem. (Balt.)*, 1923, 57, 425-435.

The fact that insulin preparations are completely inactivated by proteolytic enzymes (trypsin, papain, pepsin) indicates that the compounds present in the preparation that give the qualitative reactions for proteins are not all impurities and that insulin itself is protein-like in nature. Attempts to break down this conclusion by

other interpretative experiments have so far failed. As regards the nature of insulin it is suggested that insulin is the "effect" of a certain group or grouping. This "effect" appears to be associated with a protein on the one hand and peptones and polypeptides on the other.—F. S. H.

**The effect of parathyroid on the blood sugar curve after insulin.** Forrest (W. D.), Brit. M. J. (Lond.), 1923, ii, 916.

This report is based on a study of 5 diabetics. The fall in blood sugar following a given dose of insulin was recorded. This dose was repeated and "parathyroid" given simultaneously by mouth. In each case the fall was greater when parathyroid was used.—J. C. D.

**Parathyroid extirpation in the cat.** Nicholas (J. S.) & Swingle (W. W.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1923, 21, 160-161.

A series of 50 cats was studied. Accessory parathyroids were found to occur frequently and as far removed as the thymus. In all cases where all the parathyroid tissue was removed tetany developed. When it did not develop following operation some parathyroid tissue could be found.—J. C. D.

**Intravenous injections of calcium chloride in tetany (Les injections intraveineuses de chlorure de calcium dans la tétanie).** Rathery (F.) & Kourilsky (R.), Bull. et mém. Soc. méd. d. hôp. de Par., 1923, 47, 1482-1486.

Report of a case of classic tetany in a woman of 37. There was no morbid antecedent. The thyroid and adrenal systems were clinically intact. Medication by parathyroid opotherapy was inefficacious. Ingestion of calcium chloride diminished the attacks but failed to cause their cessation for some days. On the other hand, the intravenous injection of this compound brought about immediate relief. A combination of the two methods is advocated. One gram by the intravenous route averted the crisis, while six grams per os were necessary to give useful results.—F. S. H.

**Irradiation of the thymus in myasthenia gravis.** Mella (H.), Med. Clin. N. Am. (Phila.), 1923, 7, 939-949.

Report of a case in a colored man of 48 who died shortly after admission to the hospital. In another case occurring in a white woman of 23, four x-ray treatments over the thymus region, at three weeks' intervals, apparently restored the patient to health. It is concluded that there are cases of myasthenia gravis in which abnormalities of the thymus may be found, and that the myasthenic syndrome may follow the development of tumor of the thymus and disappear upon irradiation of the thymus region.—I. B.

Iodine content of the thyroid of the goat (*La teneur en iode de la thyroïde de la chèvre*). Arnold (R.) & Gley (E.), *J. de Physiol. et de path. gén. (Par.)*, 1923, 21, 498-504. (7)

The thyroid of the goat is very rich in iodine. It contains on the average 6.352 mgm. per gram of dry substance (minimum 1.93 mgm., maximum 8.06 mgm.). There is no relation between the iodine content of the gland and its weight in this animal. Notable differences occur in the iodine content of the two lobes of the goat's thyroid.—W. B. C.

The thyroid gland and the toxemias—with special relation to intestinal stasis. Bainbridge (W. S.), *Illinois M. J. (Oak Park)*, 1922, 41, 1-6.

A brief survey of the etiology of the common thyroid affections, with special emphasis on the rôle of intestinal autointoxication in the production of hyperthyroidism. The author realizes that there are degrees of toxic goiter yielding to nonsurgical measures. Careful search should be made in each case for toxic factors, whether they exist in tonsils, teeth, sinuses, or intestinal tract. The correction of these disorders may not only lead to cure of the thyroid condition, but may prevent many goiters from reaching the stage where surgery becomes inevitable.—I. B.

A case of myxedema with symptoms referable to the central nervous system (*Ein Fall von Myxödem mit Symptomen vom zentralen Nervensystem*). Barkman (A.), *Deutsche Ztschr. f. Nervenhe. (Leipz.)*, 1923, 78, 293.

To the 5 cases of myxedema with cerebellar symptoms previously described by Söderbergh and Odin the author adds another, a woman of 33 showing hypotonia, adiadochokinesis, and other disturbances which were held to be of cerebellar origin. The symptoms disappeared under thyroid treatment. Söderbergh postulated a toxic disturbance of the cerebellar apparatus in his cases. Barkman extends this hypothesis as follows: in myxedema there is a toxic disturbance of the cerebellar apparatus and of the central ganglia (extra-pyramidal system) to which the cerebellar symptoms and the characteristic slowness of voluntary movements in this disease are due.—*Med. Sc.*, 9, 187.

Hyper- and hypo-thyroidism, causation, prevention, and treatment. Barr (J.), *Am. Med. (Burlington)*, 1921, 27, 465-475.

According to Barr, exophthalmic goiter is due to hyperthyroidism, the latter in turn produced by the administration of iodine, emotionalism, sexual activity, and deficiency of calcium content of the blood. "Causation and prevention come before treatment, and must have primary attention. Exophthalmic goiter does not spring

up in a night like Jonah's gourd, nor does it forthwith wither away even under the surgeon's knife." The chief means of prevention is treatment when the patient is in the pre-active stage and does not present the typical evidences of the disease. A tendency to emotional and vasomotor disturbances, a warm, moist skin, active capillary circulation, high venous pressure, rapid heart action easily accelerated by physical or mental excitation, an increase of the deep reflexes and slight muscular tremor are the earmarks of early cases. In treatment of exophthalmic goiter Barr recommends spondylotherapy, the administration of calcium salts, and a liberal diet consisting chiefly of milk, farinaceous foods, white meats, olive oil, butter, and fat bacon. Surgery and x-ray treatment are not indicated. The paper includes a few brief remarks on the etiology and treatment of endemic goiter, myxedema, mastitis, adenoids, and enlarged prostate.—I. B.

Some notes on thyroid therapeutics. Berkeley (W. W.), *Internat. Clin. (Phila.)*, 1923, 33s., 3, 83-91.

A useful paper dealing with the practical aspect of thyroid opotherapy. According to Hunt, pig's thyroid contains relatively more iodine than sheep's, bull's, or man's, and is therefore the most popular in therapeutics. The bullock's thyroid, however, approaches most nearly the composition of the human gland in iodine content, and is apparently the most condensed of all the commonly available glands. Commercial thyroid gland contains less stored iodine when prepared in winter than in summer. Defects in the freezing mechanism with resulting decomposition of the glands, faulty desiccation, and even the process of fat extraction, are factors which may render the final product inert, harmful or both. Thyroxin, though in many respects a highly useful substance, probably does not contain all the active portion of the fresh thyroid gland. Though the percentage of iodine is a useful index of the probable potency of desiccated whole thyroid substance, it is to be noted that, out of several commercial preparations of the same iodine content, some are much more toxic than others. The author uses whole thyroid from which no effort has been made to extract the fat; he obtains desiccated tablets from fresh glands removed from the animal 7 hours before. With this product he obtains excellent results from very small doses, and he finds that even with the largest doses toxic symptoms are very rare. By reason of the oral administration of thyroid substance, the amount absorbed by the patient is inconstant; the most dependable criterion of overdosage is onset of the usual clinical symptoms. Contraindications to thyroid administration are conditions presenting evidences of thyroid hypersecretion, i. e., hyperthyroidism and Graves' disease. Indications for the administration of thyroid substance are many. Hypothyroidism whether frankly expressed as in cretinism or myxedema, or vaguely manifested as

mental hebetude, chronic fatigue, constipation, rough skin, hypotension, and subnormal temperature are indications for thyroid therapy. Again, thyroid opotherapy is beneficial in the diffuse goiter of puberty and adolescence, in many skin affections and in some forms of arthritis. No case of advanced myxedema or complete cretinism is ever restored to normal. It is rather in the minor deficiencies of the gland that the signal triumphs are seen. In the determination of the dosage and frequency of administration one should know the source of the preparation, how old it is, and the iodine content. The dosage in the beginning should be small and frequently repeated, and an effort should be made to determine what dosage is capable of producing symptoms of the full physiological effect. Individualization should dominate treatment. In the event that desired clinical effects fail to appear with the oral administration of a reliable preparation of dry whole thyroid gland, intravenous administration of thyroxin may be tried.—I. B.

**Effect of thyroidectomy upon the reaction of sheep to insulin.** Bodansky (A.), *Proc. Soc. Exper. Biol. & Med. (N. Y.)*, 1923, 21, 46.

Under the conditions of the experiment the reduction of the sugar content in the blood was greater, covered a longer time and was slower in disappearing than in animals with the thyroid intact.  
—J. C. D.

**Observations on the thyroid gland and its relation to the function of the pelvic organs.** Bourne (A. W.) & Wilson (C. M.), *St. Mary's Hosp. Gaz. (Lond.)*, 1921, 27, 108-110.

Cases of chronic menorrhagia of intangible etiology usually occurring in young unmarried women are commonly instances of hyperthyroidism, presenting at the same time the earmarks of susceptibility to Graves' disease. In another and smaller class of persons the menorrhagia dates back from a normal confinement; here, too, there is no discoverable pelvic abnormality, but there is an increased basal metabolism. The question arises whether this is due to post partum subinvolution of the thyroid. Of 18 patients with menorrhagia of the above types, 16 showed an increased basal metabolism varying from plus 46% to plus 11.2%. X-ray treatment of the thyroid in those whose basal metabolism was increased resulted in cure in 11 cases; 1 patient was improved, and 4 did not respond to treatment. Of the 4 patients who did not respond to treatment, in 3 it was impossible to reduce the basal metabolic rate below plus 22.7, 24, and 16, respectively, despite repeated exposures. In addition to improvement in menstruation in benefited patients, there was marked improvement in general health and in weight. One patient's basal metabolic rate was reduced to minus 13, and she showed signs of myxedema, hence the treatment is not devoid of

danger of subthyroidism. In the majority of pregnant women there is an increased basal metabolic rate. Calorimetric determinations following parturition likewise proved the existence of the tendency of these subjects toward thyroid hyperactivity.—I. B.

A preliminary report of the action of buried radium on diseased thyroids in man. Bower (J. O.) & Clark (J. H.), *Am. J. Roentgenol.* (N. Y.), 1923, 10, 875-880.

Three different types of thyroid disease are reported in which large doses of buried radium were employed. The large dose was well borne and gave no untoward symptoms. The use of buried radium needles is a feasible therapeutic measure and gives reliable results. The authors believe that radium is far superior to the injection of boiling water, quinine and urea, or polar ligation; that it is indicated in cases that are poor operative risks. Owing to the apparent resistance of thyroid tissue to radium rays, as found from experimental work, it is urged that those using radium in thyroid disease employ comparatively large doses of buried element.

—R. G. H.

Radical thyroid surgery and prophylaxis (*Radikale Kropfoperation und Kropfphylaxie*). Fritzsche (E.), *Schweiz. med. Wchnschr.* (Basel), 1921, 51, 1016-1018.

A discussion of the technic of thyroid surgery, with remarks detailing the author's experiences in the prophylaxis of goiter. A series of 332 thyroid operations without mortality is reported. Among other sequellae there occurred a varying degree of vocal paralysis in 6% of these patients. Often the diagnosis of vocal paralysis could not be made without a laryngoscopic examination. Eight patients presented evidences of damage to the cervical sympathetic, 4 of whom had already shown these symptoms prior to operation. Of 259 patients operated upon between 1913 and 1919 inclusive, 195 presented themselves for postoperative examination, and of these, 88 showed a varying degree of recurrence. The author believes that recurrence in a considerable percentage of cases is unavoidable unless total extirpation of all thyroid tissue is practiced,—a procedure which would produce myxedema. The author suggests that as serious thought be given to the prophylaxis of postoperative goiter as is directed toward goiter in general. As school physician of Glarus, a region in which goiter is endemic, Fritzsche studied the thyroids of a large series of children. In common with other observers, he points out that school life is not necessarily a cause of goiter, for enlargement of the thyroid already exists in many children prior to school age. As the children grow older the goiter becomes larger. It is also observed that the tendency toward goiter formation increases with the age of the child, so that there are more goiters to be found among older than among

younger children. Of a total of 763 goiterous children treated with minute doses of iodine, 269 were improved, 453 were unimproved, and in 41 children the goiter was aggravated. Of the cases in which the goiter continued to grow, 28 occurred in girls and 13 in boys, all of whom were either of pre-puberty or puberty age. The author recommends immediate iodine administration as a prophylactic measure against recurrence to all patients operated upon for goiter, the treatment to be continued for years. It is further recommended that the inhabitants of regions in which goiter is endemic be supplied with table salt containing iodine in such doses that each person receive approximately 0.5 gm. of sodium iodide yearly.—I. B.

**A proving of thyroid gland.** Gillingham (H. P.), Homeop. Recorder (Phila.), 1922, 37, 145, 193, 256, 302.

A series of papers detailing the physiological effects produced upon 6 young women by the administration of homeopathic doses of thyroid in tablet form.—I. B.

**The oxygen consumption of thyroid and diiodotyrosine-fed tadpoles.** Helff (O. M.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1923, 21, 34-39.

Tadpoles of *Rana pipiens* were kept in a solution of diiodotyrosine and fed desiccated thyroid at intervals. The oxygen was determined by the Winkler method. *Rana pipiens* tadpoles metamorphosed with desiccated thyroid-diiodotyrosine exhibit a progressive rise in metabolic rate as evidenced by oxygen consumption per gram weight. In stage 8 the metabolic rate reaches a maximum increase over that of stage 1 of approximately 79%. Precociously metamorphosed tadpoles increase their total oxygen consumption regardless of decreasing weight. Thyroid-diiodotyrosine-fed tadpoles undergo a gradual decrease in weight amounting to 57% in stage 8. Etherization of stage 1 tadpoles (normal animals) results in approximately 19% increased oxygen consumption.—J. C. D.

**A typical form of Graves' disease (forme fruste, interstitial goiter).** Hertzler (A. E.), J. Missouri M. Ass. (St. Louis), 1922, 19, 207-209.

The author concludes as follows: (1) there is a state in which the patient presents mild thyrotoxic symptoms associated with general neuropathic symptoms and menstrual disturbances; (2) these patients show an increase in the interstitial cells of the thyroid gland and an aplasia of the ovaries; (3) operation on the thyroid gland gives but temporary results and operation on the pelvic organs is worse than useless.—I. B.

**Hypothyroidism and the general practitioner.** Hutton (J. H.), Illinois M. J. (Oak Park), 1922, 41, 363-367.



The remarks contained in this paper are based upon observations of 10 cases of hyper- and 35 of hypo-thyroidism seen by the author during the past year. According to Hutton more than three times as many cases of hypothyroidism as of hyperthyroidism are encountered in general practice. The frequency of thyroid hypo-secretion is overlooked and many cases are unrecognized because the general practitioner is ever on the alert for evidences of the opposite condition. Hypothyroidism is frequently the major expression of a pluriglandular dysfunction requiring corresponding glandular therapy.—I. B.

**A study of basal metabolism in alopecia areata.** Levy-Franckel, Juster & Van Bogaert, Bull. Soc. franç. de dermat. et syph. (Par.), 1923, 30, 290.

Levy-Franckel and Juster have already commented on the apparent rôle of hyperthyroidism in alopecia areata, and now in a study of 22 cases, they have found the basal metabolism distinctly above normal in 14. In 5 of the remaining normal cases, thyroid had been administered previously.—Arch. Dermat. & Syph., 9, 122.

**Quinin in exophthalmic goiter.** Kleinschmidt, Zentralbl. f. Chir. (Leipz.), 1923, 50, 1425 (Sept. 15).

Kleinschmidt used quinin hydrobromid for preliminary treatment in more than 50 cases of exophthalmic goiter, and compared the results with those in about the same number in which no preliminary treatment was given. The results speak very favorably for quinin in the preoperative and postoperative treatment of this disease. The patients received, about a week before the operation and for a corresponding period afterward, two or three times daily, 0.25 gm. of quinin hydrobromid by mouth. The pulse diminished from 10 to 15 beats a minute during the preliminary treatment. At the same time, subjective and objective improvement in the existing nervousness was noted. After the operation, the pulse count rose, but, on the average, remained from 12 to 15 beats lower than the average for the patients who had received no preliminary treatment. The pulse on dismissal of the patients ranged from 80 to 81 for those who had received preliminary treatment and from 95 to 96 in the others. The quality of the pulse was also good, and post-operative excitement was rarer and less marked.

—J. Am. M. Ass., 81, 1995.

**Iodine metabolism on normal diet in relation to prevention of goitre.** McClendon (J. F.) & Hathaway (J. C.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1923, 21, 129.

The authors give figures showing the iodine content in several foods. The iodine content in wheat and oats from non-goiterous areas is much greater than that in wheat from a goiterous region.

—J. C. D.

The frequency of goiter in a region of the Bernese Jura. The etiology of endemic goiter. (*La fréquence du goître dans une région du Jura bernois. Contribution à l'étude de l'étiologie du goître endémique*). Messerli (F. M.), *Rev. méd. de la Suisse Rom. (Genève)*, 1922, 42, 1-11.

Messerli found the organ hypertrophied in the greater percentage of children. Goiter is relatively rare in the neighboring villages of the Franches-Montagnes where the inhabitants use boiled cistern water. In the valley of Tavannes the drinking water is infected and not boiled, thus accounting for the prevalence of goiter in that region. Thyroid hypertrophy in children residing where goiter is endemic appears before school age and is not dependent upon school life; it increases in frequency and in degree as puberty is approached.—I. B.

The development of goiter in children. The etiology of endemic goiter (*Le développement du goître chez les enfants. Contribution à l'étiologie du goître endémique*). Messerli (F. M.), *Rev. méd. de la Suisse Rom. (Genève)*, 1923, 42, 12-14.

The valley of la Broye, the region presenting the greatest number of endemic goiters in the section of Vaude, was studied by the author. More than 50% of the children examined at Moudon, Payerne and Avenches, aged 5 to 6 years (school entrance age), presented abnormal thyroids. In view of this fact, it is evident that prophylaxis should begin some time prior to school age. The school statistics of Moudon, Payerne and Avenches indicate that the thyroid hypertrophy increases consistently with the age of the child. The author reaffirms the results of previous researches to the effect that goiter in children in these regions is not due to school life, but is endemic in nature.—I. B.

An unusual sensitizing action of thyroid substance on the effect of epinephrin in man. Morris (R. M.), Witter (M. S.) & Weiss (S.), *Proc. Soc. Exper. Biol. & Med. (N. Y.)*, 1923, 21, 149-151.

A hypothyroid patient was given an injection of adrenin without eliciting unusual symptoms. She then took dried thyroid tablets for 7 weeks. The adrenin injection was repeated. There was a marked reaction, including a drop of the systolic blood pressure to zero, extra systoles, trembling and choreiform movements. The authors suggest that following the administration of these large doses of thyroid substance the dilator action of epinephrin on the capillary system was apparently antagonistic to its constrictor action on the peripheral arteries and arterioles.—J. C. D.

Analysis of my end-results in thyroid surgery. Porter (C. A.), *Surg., Gynec. & Obst. (Chicago)*, 1923, 36, 61.

The author analyzes all his cases that have been operated upon

since 1904, with the exception of the non-toxic goitres. There were 19 cases of malignant disease of the thyroid, 4 of which were classified as sarcoma and 15 as carcinoma. A detailed history of each case is given. The age of onset of one was 25, one 35, and of the remainder more than 45 years. The duration of the tumor previous to operation was under 2 years in five cases, 5 years in one case, and in the remainder from 6 to 28 years. A study of his series shows that there are two distinct types; one occurs primarily in patients beyond middle life and grows steadily or rapidly; the other in patients beyond middle life and arises in a tumor, probably an adenoma, of long duration, and shows evidence of the onset of malignancy by more or less sudden increase in size or in duration, with loss of weight and pressure symptoms. The particularly unfavorable cases are those in which the tumor is fixed to the trachea or causes paralysis by involvement of the recurrent nerve. The most favorable are the encapsulated adenomata with malignant degeneration. He believes that the most satisfactory treatment for this type of case is the radical operation, provided that an x-ray examination of the lungs is negative. Subsequent radium and intensive x-ray treatment is often of value and may postpone, if not entirely avoid, the need for tracheotomy. The number of toxic goitres was 204, and the operative results have shown a steady improvement. The mortality, at first 15%, had steadily fallen to 3%. The author regards this improvement as partly due to the preliminary use of x-ray treatment and quotes a series of cases in which this form of treatment used alone led to a complete cure. The operations are graded according to his judgment of the patient's condition, and may consist of preliminary ligations, hemithyroidectomy or subtotal thyroidectomy. Of the 204 cases there were 24 deaths in the hospital and 9 deaths at various periods after discharge. The deaths are divided into 4 classes: (1) hyperthyroidism, 13 in number; (2) pulmonary complications, which have been much more frequent than in the case of non-toxic goitres, 8; (3) cardiac complications; (4) so-called accidental death. In addition to these deaths, 24 cases were lost sight of. Of the remaining 147, 26 are too recent for analysis, thus leaving 121 cases that have been analyzed. Forty-five of these cases were not examined by the author, and the end results are based upon reports from the local physician or the patient. It is interesting to note that among this group there was one unimproved, 3 improved but not cured, 4 cured of hyperthyroidism but showing marked mental symptoms, and 4 showing cardiac symptoms. The remainder were cured. Of the cases examined by himself he lays special stress in determining the cure by the nature of the basal metabolic index. Of 13 ligations 11 had such an investigation carried out, and 9 of them were within normal limits; that is to say, the metabolic rate was within plus or minus 5. Of the hemithyroidectomies metabolic rate determination was carried out on 35;

32 of these showed complete cure, but although ligation and hemithyroidectomy may cure many patients, ultimate thyroidectomy most quickly and permanently reduces the metabolism to normal.

—Med. Sc., 9, 46.

**The destruction of the specific action of thyroxin by the blood in vivo and in vitro (Ueber die Zerstörung der Spezifischen des Thyroxins durch die Einwirkung von Blut in vivo und in vitro).** Romeis (B.), *Biochem. Ztschr. (Berl.)*, 1923, 141, 500-522.

Romeis used frog larvae as subjects of experimentation. It was found that if thyroxin is injected into the circulation of rabbits the feeding of tadpoles upon blood taken from them a few minutes later gave no evidence of the presence of the compound. Apparently, then, the blood destroys thyroxin rather rapidly. Liver, bile or urine from such thyroxinized animals also failed to elicit the typical thyroxin effect upon tadpoles. Similar, but not so marked changes in potency are observed when thyroxin is injected into a body cavity and later removed and tested. Repeated injections of the compound seem to result in a decrease of the destructive capacity of the blood. Similar destruction of the active principle occurs in blood in vitro and is more marked in undiluted blood. It is less the greater the amount of thyroxin added. If the blood is allowed to act upon thyroxin in vitro for 2 hours the resultant product is strongly toxic to the larvae. Shaking of thyroxin with red corpuscles is strongly destructive of the active principle; this is attributed to absorption. The results are considered as indicating the presence in the blood of a regulatory mechanism through which the incursions are maintained at optimum concentration.—F. S. H.

**Danger of iodine treatment of goiter (Ueber die Gefahren der Jodtherapie unter spezieller Berücksichtigung der modernen Bestrebungen der Kropfprophylaxe).** Roth (O.), *Schweiz. med. Wchnschr. (Basel)*, 1923, 53, 865-868.

The writer points out the danger of extreme optimism in iodine administration and of permitting its administration by laymen in the prophylaxis and treatment of goiter. In a series of cases he illustrates the advisability of careful individualization in iodine therapy of thyroid enlargements.—I. B.

**A case of toxic goiter apparently successfully treated with x-ray.** Stroud (W. D.), *Bull. Ayer Clin. Lab. Penn. Hosp. (Phila.)*, 1922, No. 7, 85-88.

A woman of 42 suffered with typical Graves' syndrome; the basal metabolism was plus 45. Shortly following x-ray treatment the basal metabolism rose to plus 66. Subsequent treatment, however, resulted in a reduction of the basal metabolism to plus 6, with a corresponding amelioration of circulatory, nervous, and other symptoms.—I. B.

**The effect of heat upon operations for exophthalmic goitre.** Walton (A. J.), *Brit. M. J. (Lond.)*, 1923, i, 1043.

In the past few years the operative results in cases of exophthalmic goitre have enormously improved, and although the average mortality remains somewhere in the region of 5%, statistics of individual operators have reduced this figure. In the last series published by Pemberton there was a mortality of only 1% in 1,093 cases. In spite of this, death will occasionally occur when least expected, and all are agreed that there is some factor at present not fully understood. The dangers of operation can be classified under three headings: (1) Those directly resulting from the disease and the effects of the disease; (2) those directly due to accidents, such as hemorrhage, pulmonary embolism, etc.; (3) those the joint result of disease and accident. However, care in the technique has done much to lessen the danger of groups (2) and (3), so that they are now no longer specially applicable to this disease. In the first group danger still remains from the fact that many of these patients do not seek operative treatment until there are secondary heart changes. The other great danger is the presence of hyperthyroidism, and although this can be much lessened by careful attention to preliminary treatment, technique of operation, and to the anesthetic, the extent of hyperthyroidism following operation is still found to be variable. Two distinct groups of cases can be recognized. The one, best described as the vascular group, occurs in young females with a large soft thyroid, marked exophthalmos, and a rapid pulse; the second, best designated as the nervous group, is seen in more elderly patients with a smaller and more nodular thyroid and more marked nervous symptoms. As a general rule the first group shows less postoperative reaction. The author has been struck by the fact that all subjects of hyperthyroidism stand heat badly, and in spite of precautions to overcome the effects of heat it had seemed that the mortality during very hot weather was abnormally high. In the present communication he analyses the results of his operations in the different months of the year, and a curve is plotted showing these results. It was found that in the months of February, March, April, May, September, October and November there was no mortality at all, but in the three months of June, July and August the mortality had risen to 20%. The figures upon which this curve was based were collected over a period of 10 years, so that this was probably not an accidental finding. Stress is laid upon the fact that in the extremely hot periods the case should be watched and operation delayed until cooler weather sets in.—*Med. Sc.*, 9, 44.

**The heart in exophthalmic goiter and adenoma with hyperthyroidism.**

Willius (F. A.) & Boothby (W. M.), with a note on the pathology by Wilson (B.), *Med. Clin. N. Am. (Phila.)*, 1923, 7, 189-219.

This important paper is based upon a study of 298 cases of

exophthalmic goiter and 79 cases of toxic adenoma. The average of the blood pressure observations made on patients with exophthalmic goiter during a period of outpatient examination were: Systolic pressure, 147; diastolic pressure, 73; pulse pressure, 74; and pulse rate, 123. In contrast to these, patients with adenomatous goiter with hyperthyroidism present showed: Systolic pressure, 153; diastolic pressure, 83; pulse pressure, 70; and pulse rate, 110. It is evident that in the latter condition a greater elevation of both systolic and diastolic pressure occurs, but the most marked difference is in the diastolic. Flushing of the skin and sweating are usually demonstrable in both conditions, but are more striking in exophthalmic goiter. There is a greater peripheral dilatation or compensatory relaxation in exophthalmic goiter than in adenomatous goiter with hyperthyroidism. Cardiac murmurs were present in exophthalmic goiter in 41% of the patients, and in adenomatous goiter with hyperthyroidism in 51%. In only 2 instances were the murmurs due to endocardial valvular diseases. The murmurs not of endocardial origin were of 2 types, both systolic in time and blowing in quality; the first had its point of maximal intensity at the third left intercostal space and was quite localized; the second was best heard at the apex and had frequently a variable transmission. Murmurs heard at the third left intercostal space are evidently functional in origin, possibly associated with changes in the blood flow, and disappear with a slowing of the circulation rate as the disease is arrested. The apical systolic murmur is probably due to relative dilatation, and invariably disappears with the termination of the disease. The capillary pulse commonly seen in exophthalmic goiter may lead to an erroneous diagnosis of aortic regurgitation, but the assumption of the presence of aortic regurgitation is never justifiable in the absence of a diastolic murmur. The hearts of most of the patients with exophthalmic goiter or adenomatous goiter with hyperthyroidism were only moderately enlarged.

Edema occurred in 21% of the patients with exophthalmic goiter, and in 20% of the patients with adenomatous goiter with hyperthyroidism. Complete rest in bed usually resulted in the disappearance of the edema except in cases of cardiac disorders. Severe cardiac damage is less common in cases of exophthalmic goiter and adenomatous goiter with hyperthyroidism than is generally believed. When present, however, it forms a dominant factor in the prognosis and treatment. The incidence of auricular fibrillation in exophthalmic goiter was 22%, while in adenomatous goiter with hyperthyroidism it was 24%. The intensity of the disease, as measured by the basal metabolic rate of patients at the time they come under observation, does not in itself greatly influence the severity of the auricular fibrillation. The duration of the disease is the more important factor in the development of myocardial damage.

Premature contraction occurred in 14% of the patients with exophthalmic goiter. In 28 of the patients the origin was in the

ventricles, and in 5, in the auricles. Paroxysmal tachycardia is not a common disorder in thyroid disease. Only 1% of the patients with exophthalmic goiter develop the condition, and in no instance was it observed in patients with adenomatous goiter with hyperthyroidism. The types of paroxysmal tachycardia were auricular flutter and nodal tachycardia.

In a consecutive series of 23 deaths, including postoperative deaths as well as deaths before operative intervention was possible, there was only 1 in which the heart could be considered the major contributory cause. This patient had general anasarca, was dyspneic and cyanotic, the heart was markedly enlarged, and the auricles persistently fibrillated throughout the period of observation; at no time was operative intervention considered. Because the postoperative hyperthyroid crisis is more prone to occur in patients with a high degree of hyperthyroidism, especially when associated with the irritability, mental instability and depression characteristic of exophthalmic goiter, and because the intensity of the reaction and the number of deaths are decreased by the administration of iodine, as shown by Plummer's recent investigation, it is probable that the reaction is dependent on a peculiar intoxication caused by the presence in the body of an excess of an incompletely iodized thyroid secretion and is therefore avoidable. The intensity and character of the toxemia and not the condition of the heart are the major factors in producing death.

Of the hearts of the 21 subjects which came to necropsy some degree of hypertrophy was noted in 16. This was marked in 2 instances in which the heart weighed 500 and 550 gm., respectively. The hearts were both in large females, one with exophthalmic goiter and the other with nodular goiter associated with an acute terminal fibrinous pericarditis. The hypertrophy in the other instances presented from 5 to 10% increase in weight. In 2 of the hypertrophied hearts fibrosis was present.—I. B.

# Endocrinology

## *The Bulletin of the Association for the Study of Internal Secretions*

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### INDIVIDUAL CONSTITUTION AND ENDOCRINE GLANDS\*

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Experience has long taught us that important branches of science in the beginning of their development are likely to be overestimated. In the history of medicine there are numerous examples of this psychological phenomenon. Cellular pathology as well as bacteriology and, lately, also endocrinology are prominent instances. Wherever unexplainable facts or conditions occur, attempts are usually made to clear them up by means of the newly developing science, taking mere hypotheses for established facts. In such a period of marked confusion of ideas it seems permissible to exercise a certain amount of criticism and, where possible, actually to revise and to correct certain existing opinions. Especially with regard to endocrinology it would appear useful to point out in our discussion some new or at least insufficiently emphasized views.

It is a well known fact that the general habitus of young male individuals undergoes characteristic changes when they

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The cited literature is to be found in J. Bauer, *Konstitutionelle Disposition in inneren Krankheiten*. J. Springer, Berlin, 3 edit. 1924, and J. Bauer, *Vorlesungen über allgemeine Konstitution und Vererbungslehre*. J. Springer, Berlin, 2 edit. 1923.



measuring the length from the top of the head to the superior border of the pubic bone and comparing it with the length taken from the superior border of the pubic bone to the sole of the foot. The former measurement is spoken of as the "superior length," and it surpasses considerably the latter, which is spoken of as the "inferior length." In normal adults these two distances are approximately equal and the entire length of the body corresponds nearly perfectly to the reach of the outstretched arms. In pure cases of eunuchoid tallness, we find the reach of the outstretched arms to be usually greater than the body length in consequence of the extreme length of the extremities

In pure cases of eunuchoid obesity (Fig. 2) the localization and distribution of the subcutaneous fatty tissue is the characteristic feature. Accumulation of fat around the hips, in the lower abdominal region especially above the genital organs, in the buttocks, breasts and thighs, resembling closely the fat distribution of normal females, characterizes this type of eunuchoidism. Border line cases between these two groups are not infrequent.

The fact that the same primary defect of the male genital organs may be followed by two different types of abnormal development and growth shows that the results of insufficient secretion of the genital hormone are determined not only by this fact alone but also by something else situated in the rest of the body, namely, by the special kind of reaction of the organism to the genital insufficiency. It is generally assumed that the quality and reactivity of all the rest of the endocrine apparatus may explain the different results of a primary hypogonadism. Individuals with a rather well developed and functioning hypophysis, with a certain constitutional tendency to pituitary, and perhaps also to thyroid hyperactivity, would become eunuchoid giants; individuals with a less developed and active hypophysis, with a slightly exhausted pituitary and perhaps also thyroid function, would show the characteristic signs of eunuchoid stoutness.

This explanation seems at first sight quite evident, but it is decidedly unsatisfactory when we consider a number of obvious facts. First, we could not explain the border line cases mentioned above, where characteristic features of eunuchoid tallness with eunuchoid obesity are combined, for we cannot assume a

hyper- and a hypo-activity of the pituitary gland at the same time.

A second fact would seem to be particularly interesting. The eunuchoid skeletal proportions are usually explained according to Tandler and Gross by the abnormal persistence of non-ossification of the epiphyseal junctions in the long bones of hypo-



Fig. 3. Eunuchoid proportions in a 12 year old girl (after Stats)

genital persons. When the ossification of these junctions is delayed, the longitudinal growth may persist for a longer period and the natural consequence would be the overgrowth of the extremities, that is to say eunuchoid proportions of the body,

provided a sufficient activity of the pituitary and thyroid glands is present in order to stimulate the growth in general.

This theory however cannot satisfy any longer since, as I have pointed out, eunuchoid skeletal proportions are sometimes to be found even in dwarfs, especially in hypopituitary dwarfs, as well as in children whose epiphyseal junctions are not yet ossified at this period of life. (Fig. 3.) Disproportionate length of the extremities can therefore not be explained solely by a longer duration of longitudinal growth on account of delayed ossification of the epiphyses; that it can exist also when there is an insufficient function of the pituitary gland is quite obvious. There must still be something besides the endocrine glands which governs proportionate growth and which may be responsible for eunuchoid proportions of the body under certain conditions. We are forced to assume that the cells of the osseous system and especially the cells forming the epiphyseal part of it must have their own power of proliferation and of growth, although they may be influenced by certain hormones. Were we able to eliminate the endocrine glands we would be obliged to acknowledge a certain autochthonous automatism of the bony tissue itself. The endocrine organs influence the growth, but they alone do not bring it about; without them we would observe a certain amount of growth too. Normal growth is the product of co-operation of autochthonous growth of the skeleton cells with certain endocrine glands stimulating or checking it. The autochthonous power of growth, however, is to a high degree a constitutional characteristic of the individual, it is transmissible by inheritance and must therefore be potentially localized somewhere in the germ cells. Otherwise we could not explain, for instance, the great racial and family differences of growth<sup>1</sup> and body length; but especially we could not explain the marked eunuchoid proportions of some negro races that show no signs of hypogenitalism, but on the contrary, possess larger genital organs than are usual in white races and reach puberty generally much earlier than the latter.

We may sum up the facts as follows: eunuchoid proportions of the body cannot be explained merely by delayed ossification of the epiphyseal junctions of the long bones and hyperactivity of pituitary or thyroid; the constitutional autochthonous tendency of growth of the bone cells themselves must be considered

as an important, individually different, factor determining not only the definite body length but also the body proportions. There must exist, however, a certain relation between the insufficient or absent endocrine genital function on the one hand and the increased tendency to longitudinal growth of the extremities on the other. It is very probable that the genital hormone checks directly this longitudinal growth, but the results of the insufficient or absent genital hormone are not only dependent on the absence of this checking influence, but primarily on the constitutional growth-power of the bone cells themselves. When this constitutional growth-power is very high, then eunuchoid proportions may be observed also without a genital insufficiency, notably in negroes (as a racial characteristic) and in certain children: when it is moderately high, but not extreme, then the absence of the checking genital hormone alone may produce the characteristic eunuchoid proportions; when it is only slight, then not even the lack of this checking influence will be sufficient to increase the length of the extremities. The loss of the specific genito-hormonal inhibitory influence upon the longitudinal growth of the extremities can become manifest also in pituitary dwarfs in whom the general growth of the body is diminished by the absence of a hormonal stimulus. It can be paralyzed, however, by the lessened autochthonous growth in cases of general under-development, or general growth insufficiency, and in cases of so-called universal infantilism, where a certain degree of hypogenitalism is only a part of the general hypoplasia, just as the small genital organs of a child correspond to the size and development of the whole body. Just as a child usually does not show eunuchoid skeletal proportions, so they are absent in cases of universal infantilism.

A thorough analysis of a quite different state of constitutional growth disturbance, of the so-called chondrodystrophia or achondroplasia, and of its rudimentary type, chondrohypoplasia (Fig. 4), reveals another connection between the longitudinal growth of the extremities and the development and functional activity of the genital organs. Chondrodystrophic dwarfism is characterized, as is well known, by more or less extreme shortness of the extremities entirely out of proportion to the trunk

and head. Those dwarfs often show marked signs of hypergenitalism. Their external genital apparatus is disproportionately large, puberty is reached early, and the activity of their sexual organs is sometimes extremely high. The secondary sex characters are usually very well developed and several authors have sought also the explanation of the strong development of the musculature, the high intelligence, and the peculiar hypomaniac mental state in a primary hypergenitalism. It is well known that achondroplastic dwarfs were especially used as court jesters and are at premium as clowns. Therefore, a great number of authors (among them Poncet and Leriche, Lauze, Bertolotti, Parhon, Rebattu, G. A. Wagner) have suggested primary hypergenitalism as the cause of this growth anomaly. This suggestion, however, is unacceptable.

The shortness of the extremities in achondroplasia cannot be due to a hyper-production of the genital hormone checking especially the longitudinal growth of the extremities, since this shortness is to be found even in new born children. It is certainly due to a constitutional anomaly of the skeletal cells themselves, to a hypoplastic state of the cells at the epiphyseal junctions determining the longitudinal growth by their activity. Anatomical researches, especially those of Kaufmann, have demonstrated the abnormal state of these cells; sometimes they are markedly hypoplastic, sometimes altered in a more severe way—irregular, or showing a mucoid degeneration. This severe type of the so-called malacic chondrodystrophia is to be observed only in new born children, since such individuals are usually not able to remain alive. Cartilaginous exostoses near the epiphyseal borders, often found in achondroplastic dwarfs, demonstrate also the primary abnormal state of the bone tissue in certain parts. Of particular importance, however, are the rare cases of hemilateral achondroplasia, or partial achondroplasia, where only one side or only one extremity is affected by this anomaly. (Fig. 5.) It is quite impossible to explain these peculiar conditions by a hormonal influence that must manifest itself in the whole body and could never bring about such a partial deficiency.

Neither the increased check of the longitudinal growth by the genital hormone nor a premature closure, that is ossification

of the epiphyseal junctions, can therefore be the cause of the disproportionate shortness of the extremities in achondroplastic dwarfs. Regarding the last point it may be mentioned that Japanese commonly cease to grow long before the appearance of puberty, just the contrary of what we have stated before of some negro races. And yet a certain relation between insufficient longitudinal growth of the extremities and hypergenitalism is not to be denied. The cause of the hypoplastic state, of the

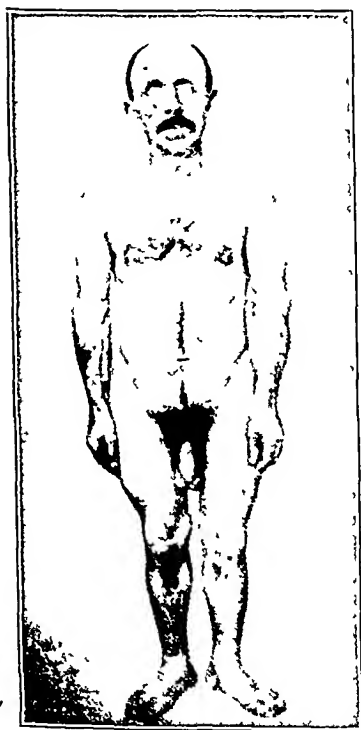


Fig 4 Chondrohypoplasia

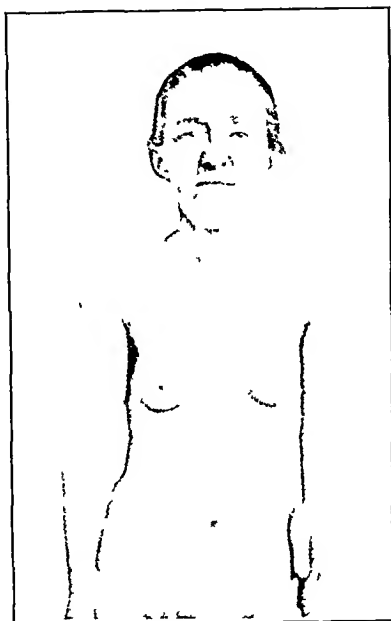


Fig 5 Partial achondroplasia

insufficient activity of the cartilaginous cells in the epiphyses of a chondrodystrophia, is an abnormal constitution of these cells due to an abnormal state of the germ cells as chondrodystrophia is a typical hereditary pathological condition.

According to the well known doctrine of modern heredity, which we owe primarily to the admirable investigations of Morgan and his associates, we must assume that in a certain part of

the chromosomal apparatus of the fertilized ovum there exists somewhere an alteration, an abnormality, which represents the abnormal state of the special skeletal cells in the fully developed individual. To the constitutionally and hereditarily abnormal state of this part of the body and particularly of the skeleton there must correspond an abnormal state somewhere in the chromosomal apparatus (with its probable 12 chromosomes) in the mature human germ cells. It seems necessary to recall that these 12 chromosomes represent very probably the totality of transmissible qualities that are to be imagined as localized in some way in these little bodies. It is impossible and surpasses the limits of natural science to attempt a more detailed explanation of this fact. But what is settled as a matter of fact in the general science of heredity is to be applied also to the human organism. Further, we have to remember that during the evolution of the whole organism from a single fertilized ovum, a part of every one of these chromosomes later enters every new body cell. The marvellous mitotic cell division provides for the equal distribution of the chromosomal material to every one of the new cells. Every cell of our body possesses, therefore, the same chromosomal material as the fertilized ovum from which our body originated. But this chromosomal material represents at the same time the potential power of specific differentiation of the cells, providing innumerable new cells and forming in this way the different parts of our body. The specific structure of the chromosomes with their potential power to bring about quite a specific differentiation of the cells and cell complexes is responsible for the characterization of the species, race, family, sex and a great many of the individual peculiarities which are potentially determined and fixed at the moment of fertilization. Every cell of the body gets the same amount of chromosomal material by the mitotic cell division, but the potential power to bring about quite a definite differentiation of the cells with quite definite and specific characteristics—this potential power has become effective during the developmental process and has been used up to a different degree, depending upon the different final state of the cells. We call the great number of different latent characteristics (localized somewhere in the chromosomes) unit-

characters or Mendelian units, as they are transmitted to the descendants according to the rules of Gregor Mendel.

But what we assume to be the material substratum of those units must be present, therefore, in every body cell. The units responsible for the development of a particular body length, of a particularly long nose, of musical endowment, or of red hair will be present in every cell of the body, but they will be efficacious in a quite different way in the different cells. The units for body length will manifest themselves in the cells of epiphyseal cartilages, the units for a long nose in the cells forming later the constituents of the nose, the units for musical talents in certain brain cells and the units for red hair in the cells producing the hair pigment. In the remaining cells of the body all these different units stay inactive and latent, only in the germ cells they keep their whole latent power undiminished, in order to manifest it when the germ cell happens to meet with a second germ cell of the other sex. We may speak of units as chromosomal potencies, which are present in every cell but which become active only in a few special cell-groups, according to the kind of these units. In lower organisms where the power of regeneration is higher or even complete, the presence of all units in every cell is quite obvious. The chromosomal potency representing the Mendelian units is the highest known, almost incomprehensible, store of potential energy.

After this digression from our subject we may return prepared to apply to it the statements of the general science of heredity. In a certain part of the chromosomal apparatus there must be localized the constitutional tendency and power of the epiphyseal cartilaginous cells of the long extremity-bones to proliferate, to grow, and to bring about a certain proportionate length of the limbs. In the pathological condition of achondroplasia this tendency and power is diminished. But according to our former statements bearing upon the relation between achondroplasia and hypergenitalism and corresponding to the experiences and interpretations of the general science of heredity we must assume that these two constitutional anomalies are very often associated with each other, because their chromosomal localizations lie close together and, therefore, either both are often affected with an anomaly at the same time, or the cor-



responding units have a certain influence not only upon one but also upon the other of the two characters. One uses for this phenomenon the term pleiotropic units. We speak of this as a *germinative or chromosomal correlation* and must suppose that such a correlation exists between the unit governing the longitudinal growth of extremities and the unit governing the development of the genital apparatus.

An entirely analogous chromosomal correlation is to be observed, for instance, between a constitutional fragility of the bones (the so-called osteopsathyrosis idiopathica) and a thin blue sclera, or, according to my own investigations, between red hair and freckles. The tendency to become freckled, particularly at places that are usually not exposed to sunlight as the nape of the neck or forearms, is certainly correlated with the tendency to red hair pigment in the chromosomal apparatus, because we find not only the combination of red hair with freckles in the same person, but often separated from each other in different individuals of the same family. A patient of mine with dark and partially gray hair but with numerous freckles at the nape of his neck was rather surprised when I asked him who in his family had red hair. His sister had, as a matter of fact, fox-red hair!

In our case of correlation between the chromosomal potency for longitudinal growth and that for genital development, this germinative chromosomal correlation is associated with a real hormonal correlation, as we pointed out before with regard to the checking influence of genital hormone upon the longitudinal growth. This peculiar kind of double correlation, germinative and hormonal, is to be observed also in other instances, particularly the correlation of the development of the genital glands and that of the so-called secondary or accessory sex characters.

According to the most interesting facts revealed by experimental and clinical endocrinology the consideration is usually ignored that this correlation cannot be a pure hormonal one, but that the genital hormones have only a stimulating, increasing, or as Halban called it twenty years ago, a protective influence upon the development of the secondary sex characters. But those characters are established and fixed potentially at the same moment as the sex of the genital glands and the genital organs; they are correlated with them in the germ; there exists not only

a hormonal but also a chromosomal correlation between them. The striking fact, that the so-called secondary sex characters can be influenced and under certain conditions even abolished by removal of the genital glands, that by implantation of heterosexual genital glands on castrated guinea-pigs even some heterosexual characters may be provoked (Steinach)—these facts well known and easily to be understood as a consequence of hormonal correlation hide to a certain degree a number of facts pointing towards a germinative correlation between genital glands and secondary sex characters.

According to the well established studies of the science of heredity, sex is determined at the moment of fertilization of the ovum by a certain constitution of chromosomes. But determination of sex does not mean merely testicles or ovaries, but to a certain degree also, all other characteristics of the body and soul that are different in the two sexes. Long before puberty we recognize the typical male or female temperament. Boys are more frolicsome and noisy; girls are neat and vain; boys play at soldiering or fighting; girls prefer dolls and taking care of smaller children. Experienced pediatricians are able to recognize boys or girls in new born children solely through a somewhat different shape of the face and head. If one object that testicles and ovaries have to fulfill their endocrine functions long before puberty and even during intrauterine life, then I should ask him why a large number of secondary sex characters, such as voice, hair-growth, fat distribution, libido and so forth, do not develop before puberty associated with a marked growth of the genital glands.

But the most valuable fact is in any case the observation of Keibel and Mall, who showed that a secondary sex character such as the greater depth of the recto-uterine excavation in females is to be found in the fetus before the primary sex characters (the genital glands) are developed.

The secondary sex characters are therefore associated with the primary not only through the hormonal influence of the glands but also through a chromosomal correlation. In lower animals, for instance in insects, this latter is the only existing, as the hormonal correlation develops later on in the phylogenesis. In insects, no influence of the sexual glands upon the sex characters is to be observed. In higher animals, the genital hormone

stimulates and protects the chromosomal potency to bring about the characteristic sexual signs in the different parts of the organism. But, despite this obvious endocrine function, it must never be forgotten that every cell of the organism obtains its definite sex peculiarity from the moment of fertilization of the ovum, that a certain chromosomal structure is responsible for the sex in every one of the body cells. Of course a sexual difference will not be manifest in the cells of the liver or of the lungs, but it will be quite obvious in the cells that produce the hair, those that form the breasts and so forth.

All the different kinds of intersexuality are to be understood only by the supposition that some developmental malformation, some chromosomal disturbances had taken place some time during the development in certain cell groups. By the interference of those chromosomal anomalies with the hormonal stimuli the different types of intersexuality are to be explained. That such a chromosomal disturbance may happen somewhere during the individual development is much less astonishing than the experience that those disturbances are to be observed so seldom.

Nobody will doubt that a case of real hermaphroditism (possession of testicles and ovaries at the same time) cannot be understood through the assumption of a hormonal anomaly. The development of both sorts of genital glands in a single individual can be the result of a primary chromosomal disturbance only. Using the known formulae of the general science of heredity, we may assume that every female cell has acquired from mother and from father the equal amount of power for developing female and male characters, but that the female power under those conditions is always predominant over the male. A male organism would have acquired from his father only the power to develop male characters and since two male determinants prevail over one female, the evolution goes in the male direction.

The science of genetics and heredity is well acquainted with the fact that the prevailing power of a unit over its so-called allelomorph, in our example for instance the prevalence of F over M, or the prevalence of two M's over one F, is not an absolutely constant and unchangeable fact, but may vary within certain limits and may be dependent on different endogenous or

exogenous conditions. This variability of prevailing power is the real basis of the different kinds of intersexuality. If through an unknown cause in an individual of the female structure (FM) (FM), or of the male structure (FM) (M), the normal predominance of one F over one M, or of two M's over one F, be absent, if both tendencies become manifest and bring about at the same time true female and male characters, then the different cases of intersexuality are the consequence of the chromosomal anomaly. The famous experiments of R. Goldschmidt on butterflies (*Lymantria dispar*) are the basis for this theory.



Fig. 6. Hemilateral gynecomastia.

The highest degree of intersexuality, the result of an absolute absence of a prevailing relation between allelomorphs F and M, is the real hermaphroditism with testicles and ovaries at the same time. Lower degrees are cases in which disturbances in the sexual differentiation of the organism are due to an insufficient prevalence of the sexual allelomorphs and are to be found only in certain parts of the organism. In those cases only one sort of genital gland has developed and its sexual hormone augments the primarily insufficient prevalence of one sexual principle. Different types of pseudo-hermaphroditism and lower

degrees of intersexuality such as gynecomastia, hypospadias, heterosexual type of crines pubis, homosexuality and so on, are the natural consequence of the interference of the abnormal chromosomal sexual potencies with the hormonal influence of the sexual gland.

The abnormal chromosomal sexual potency due to an abnormal structure or to an abnormal prevailing relation between the sexual allelomorphs need not be generalized as originating from the fertilized ovum but may be present in quite exceptional cases only in certain cell groups of the organism caused by some disorders in the mitotic cell-division during the developmental period. Remarkable is not the possibility of those events but only their rarity, when we consider the highly complicated and minute process of mitosis.

Figure 6 shows a boy of thirteen with a female breast on one side only. Its appearance, shape and consistency is absolutely the same as that of a girl of eighteen. The other side of the boy's chest and the other parts of his organism, especially his genital organs, are quite normal, apart from a marked psoriasis at the knees and a persistent lanugo over the back. The boy shows quite obviously a pronounced heterosexual characteristic, but it is limited entirely to one organ and to one side. It would be quite impossible to explain such a type of intersexuality by abnormal hormonal influence, which could never produce hemilateral effects. Another photograph (Fig. 7) of a male shows an analogous lateral difference in development of another secondary sex character. This man has normally developed hair over the right side of his chest, but has no hair over the left side. Hair on the chest is a marked male secondary sex character, which is in this case developed only on one side and is absent on the other. The man has been observed by my friend Prof. Grote in Halle. I myself saw quite the same hemilateral development of the chest hair in a tuberculous patient at the City Hospital in Buffalo.

Such observations of lateral differences in secondary sex-characters are to be explained only by the supposition of an autochthonous anomaly in the chromosomal apparatus of the concerned cell-groups and never by an endocrine influence; and they illustrate very clearly the necessity of considering the autochthonous sexual constitution of every cell in the same way

as the hormones of the genital glands. They resemble completely some rare observations in animals, especially in birds, in which the animal was on one side male and on the other side a female in every respect. The term "lateral hermaphroditism" has been used for such exceptional malformations.

Thus far we have considered only the co-operation of the chromosomal sexual constitution with the genital endocrine hormone; we have now to add that the cortical part of the suprarenals and probably the pineal gland participate in influencing the sexual differentiation and that the pituitary and thyroid glands and all other endocrine glands may exert some influence upon the development of secondary sex characters by their inter-

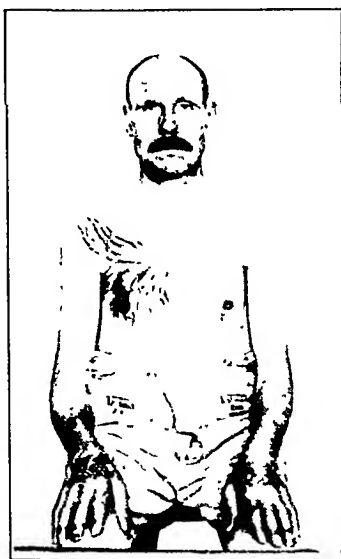


Fig. 7. Hemilateral development of chest hair.

relation with the genital glands. But in no clinical analysis dare the rôle of the chromosomal constitution be neglected. The endocrine organs do not produce, they only influence; they augment or check the chromosomal potency of sexual differentiation.

In the same way as in the origin of the body-length and body-proportions, as well as in the origin of secondary sex characters, the interference of chromosomal and endocrine effects is to be considered in the problem of fat deposition, of evolution

and of senile involution of the organism and in many other problems. Everywhere we meet with the endocrine organs as a sort of multiplier and condenser of certain chromosomal potencies. The continuously increasing complication of differentiation of the cells in the higher organisms during phylogenesis has created a special apparatus for the regulation of certain chromosomal powers, which are present in every cell, but effective only in certain cell-groups. The organs of this apparatus are the endocrine glands and, in part, the nervous system, which directly and through the intermediation of the endocrine organs has acquired an influence upon certain autochthonous potencies of certain cell-groups.

When we recall the fact that in a great number of cases the loss of the endocrine function of the testicles, either by castration, destruction or primary hypoplasia, is followed by a peculiar sort of fat deposition which we call the eunuchoid type, then we must assume that the male genital hormone has a certain influence upon the fat metabolism in quite definite parts of the subcutaneous tissue. It is here of less interest whether a generalized obesity, that is a marked general increase of fatty tissue, is the result of the hypogenitalism or not; the principal point is the affinity of the eunuchoid's or eunuch's fat for certain parts of his body (lower part of abdomen, hips, buttocks, breasts and thighs). The male type of fat-distribution has been transformed into that of the female. We do not observe an analogous change of fat-distribution in a spayed or eunuchoid woman. She may become stout or not, but the fat-distribution is not altered; it remains the same as it was before. According to this observation we must assume that the hormone of the testicles only, not that of the ovaries, exerts a checking influence upon the fat deposition in certain regions of the body; it must check in some way the lipophilia or lipotropia of these places.

The terms lipophilia or lipotropia are not merely useless paraphrases of our observation but they are really existent facts. There are in the literature some very striking clinical observations that prove indubitably the fact of a different lipophilia or lipotropia in different parts of the subcutaneous tissue. Thus, a young girl suffered from a burn on the back of her hand, and the defect had been covered with a transplanted piece of the skin of the lower abdominal region. As the girl grew up, married

and became rather stout, the fatty layer of the transplanted skin at the back of the hand did not increase in the same way as at the symmetrical site in the other hand; but it increased much more—just as much as the subcutaneous fat in the lower abdominal region whence this skin-flap had originated. That is a proof that every place on the body surface has its own specific tendency to capture and fix a certain amount of fat and that this regional lipophilia remains unchanged even after many years in transplanted skin.

The lipophilia of the subcutaneous tissue is a constitutional chromosomal character, but it is influenced by the testicle-hormone. The testicles diminish the lipophilia in certain places of the body, and we can observe that the absence or insufficiency of their function is associated with the female type of fat-distribution. The knowledge of this fact seems to be particularly important in cases of infantile obesity—fat boys before puberty show generally this female or eunuchoid type of fat distribution, as the endocrine influence of their testicles upon the lipophilia of the subcutaneous tissue has not yet developed. It is quite wrong to refer, as has been customary, in those cases of infantile obesity to a genital or perhaps primary pituitary origin of the obesity on account of this particular fat distribution. The genital organs may develop later in time and functionate quite normally, but as long as they were not yet functioning and therefore not yet checking the lipophilia at definite places on the body-surface, the fat distribution follows as a rule the feminine, eunuchoid—or better—asexual type.

On this occasion I should like to mention that the different types of fat distribution in grown-up females are not at all due to different endocrine disorders or to different functional activities of the endocrine glands, but are due solely to the different constitutional, chromosomal lipophilia of the body-areas. I am obliged to emphasize this fact in opposition to a considerable number of authors, who attribute different types of fat-localization to different endocrine types, for example, to a hypogenital or to a hypopituitary state. There does not exist a single proof for this supposition.

I have separated especially four main groups of female fat-distribution due to differing chromosomal lipophilia of the spe-



cial parts of the body-surface. By far the majority of women belong to the first group which I have called the "Rubens-type" and which is characterized by the predominance of fat localization in the lower abdominal wall, hips, loins, buttocks and thighs. The second group I have called the "breeches-type"; this type has its fat chiefly or exclusively in the trochanteric region of the thighs. The third group exhibits a marked contrast between the rather stout superior part of the body (thick arms, neck, and fatty breasts) and the thin abdomen, pelvic region and legs. The fourth type on the contrary has disproportionately stout legs and hips associated with a thin upper half of the body. Some special subtypes are represented by women with disproportionately fatty breasts or with the so-called steatopygia (extremely stout buttocks), a common racial character in some negro races.

These different types of fat distribution are not due to different endocrine constellations, but certainly depend upon a different regionary lipophilia of the subcutaneous tissue. Whether a woman should get stout or not may be partially due to her endocrine constellation, but whether the fat is distributed on the body-surface according to the first or one of the other types—that is determined solely by the autochthonous chromosomal lipophilia of the special regions.

Though I said that the development of an obesity *may* be due to an endocrine disorder, it must be added that the same kind of endocrine trouble is not always followed by the same clinical consequences and particularly not by the same degree of obesity. There are cases in which castration in a female produces a marked obesity, but I know of other cases in which no increase of weight has occurred after the removal of the ovaries. Especially do I remember a mother and her daughter who had both lost their genital glands by operation on account of a cystic degeneration of both ovaries; not only did they fail to develop any obesity, but both became markedly emaciated after the operation. It is not a single endocrine gland only, but the total of all of them combined with the constitutional chromosomal reactivity of every body cell that determines the consequences of an endocrine trouble and determines the varying clinical symptomatology following such an endocrine disturbance.

We know of a pathological state designated "progressive lipodystrophy," which is to be understood only by assuming a pathological relation and change of the lipophilia of different regions of the body surface. Such cases are characterized by a marked decrease (up to a complete disappearance) of the fatty tissue in the superior half of the body, especially in the cheeks, associated with an increasing obesity limited to the legs, hips and buttocks. Neither characteristic nor always identical endocrine changes are to be found in these cases, and when some endocrinopathic features are present, they are certainly not the cause of the pathological condition of the fatty tissue but are concomitant signs of a more generalized abnormal chromosomal structure, or, briefly, of an abnormal individual constitution.

The most interesting examples of interference of chromosomal with incretory influences are to be observed in the clinical pathology of development and involution of the body. Insufficient function of the thyroid, pituitary, genitals, and thymus at an early age is associated with developmental anomalies, with the persistence of certain infantile characters, but all of these cases are by their special symptomatology different from the rare cases of generalized hypo-evolution of so-called "universal infantilism." Just as a child does not differ from an adult by mere endocrine insufficiency of one or more glands, so universal infantilism is not due to a primary endocrine trouble but to a general cessation of development affecting every cell of the body. The hypoplasia of the endocrine organs is in those cases not the cause of the infantilism but a part of the general hypoplasia.

We know of a special type of dwarfism that is certainly also not due to an insufficient function of one or of several endocrine glands, although an early insufficiency of the thyroid as well as of the pituitary or the thymus can give rise to a type of undergrowth or dwarfism. But the so-called "primordial dwarfs" (v. Hansemann) are creatures whose single anomaly is their smallness. They are in every respect well and proportionately developed, show proportionate genital organs with normal function, are of normal intelligence and look like a miniature of a normal individual. Qualitative trouble is absent entirely. Primordial dwarfism is always hereditary and in certain negro races it is a racial characteristic. There can be no doubt that it is not

an endocrine anomaly, but only a chromosomal anomaly of the whole organism that is the real cause of this peculiar kind of dwarfism.

Certain units are to be assumed as regulating the qualitative evolution as well as the quantitative growth of the organism. An anomaly of these units brings about sometimes universal infantilism, sometimes primordial dwarfism. As these special units for evolution and growth are effective particularly on certain endocrine glands whose function is somewhat like a lubri-

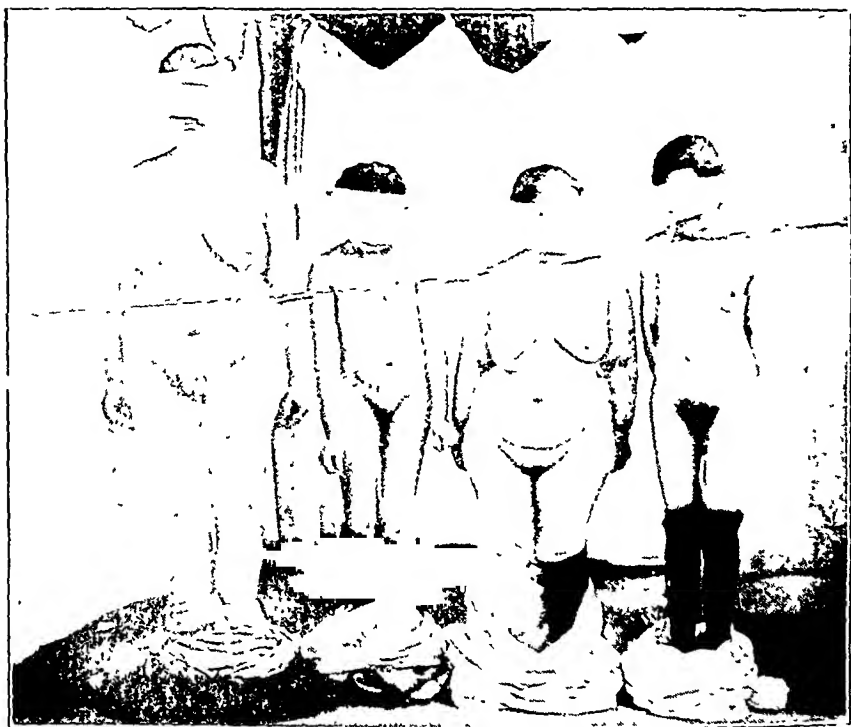


Fig. 8. Family with different kinds of growth trouble.

cant and multiplier of these units, we shall not be astonished to meet with the most different kinds of trouble, due partially to a generalized chromosomal and partially to an endocrine insufficiency. This view alone can elucidate a great number of the disturbances of growth and evolution met with in daily practice. Of particular interest in this respect are some observations on alternation of the different types of evolutionary and growth troubles in different members of one family, revealing the existence of a primary chromosomal anomaly.

P. Stewart, for instance, describes a young man of twenty affected with a general myoclonia. His growth had been completed at fourteen. Though his genital organs developed, the hair remained infantile. One sister of this patient did not grow any more after her twelfth year, but menstruated regularly after her fourteenth year; five brothers and sisters were born prematurely on account of their quite abnormal size at birth. Observations of partial or universal gigantism in one member, and of dwarfism, of acromegaly, of eunuchoidism and of other endocrine disturbances in other members of the same family have been described several times in the literature. Certain endocrine glands seem to be, in those families, points of lowered resistance and show a marked tendency to be affected either by neoplastic or, as certain observations illustrate, even by a tuberculous process.

Fig. 8 shows a mother with her three daughters. The first (from the left side) is a daughter of normal size and development. We may observe the identical kind of fat deposition (especially the cuff-like fatty masses over the wrist) in the daughter and in the mother (the third from the left in the picture), who represents a chromosomal type of dwarfism. The second from the left is a thirty-nine-year-old daughter with a pituitary and chromosomal dwarfism who exhibited an extreme degree of genital hypoplasia, eunuchoid body proportions, absence of secondary sex characters and amenorrhoea. The third daughter on the right is to be diagnosed as a chromosomal undergrowth with some features of rickets.

Fig. 9 shows a pituitary dwarf seventeen years old, an identical twin whose brother is affected by the same kind of disturbance of growth and evolution. The chromosomal character of this pituitary anomaly is therefore quite indubitable.

Very interesting is also an observation of Dr. R. Wagner at Prof. Pirquet's Children's Clinic in Vienna; he describes two brothers at the age of three and three and a half years, respectively, both affected with a marked premature development, corresponding to a precocious puberty. As signs of an intracranial and especially of a pineal lesion as well as of a suprarenal anomaly were not to be detected, a chromosomal anomaly, more or less:

limited in its manifestation to the genital organs, is to be assumed in those two brothers. Although in certain cases of premature development a primary pineal or suprarenal disorder may be the cause, we have to consider the cases, in which either marked changes such as aplasia of pineal had been present with-

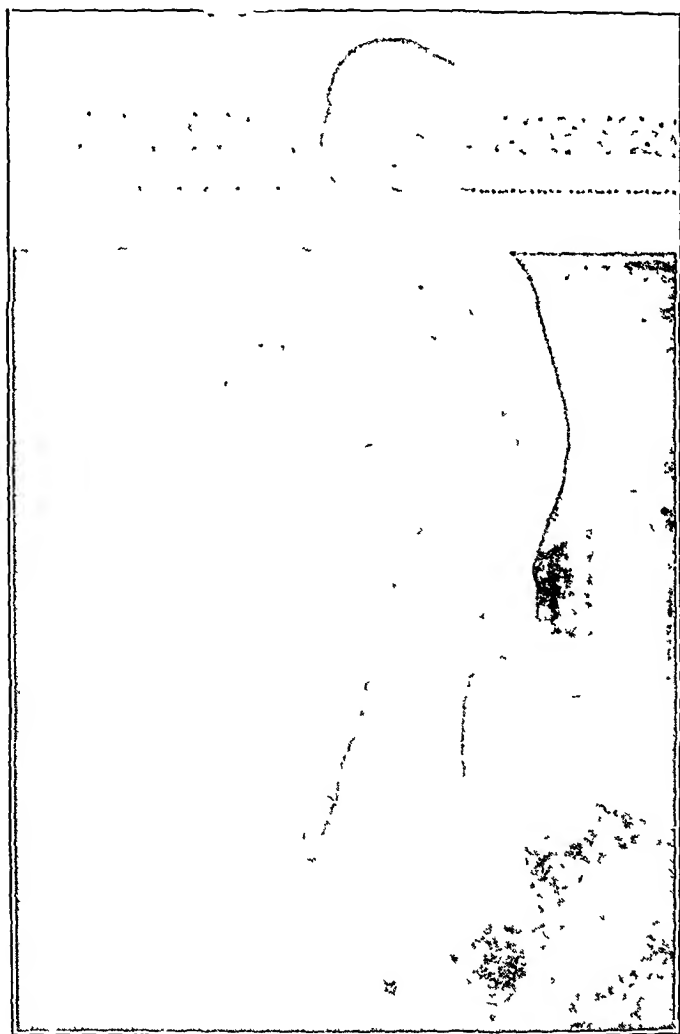


Fig. 9 Pituitary dwarfism in an identical twin of 17 years

at a premature development or in which a precocious puberty appeared apart from any pathological condition of the pineal gland (Krabbe). The observation of the Viennese Children's Clinic illustrates in an obvious way the constitutional chromosomal character of some cases of this developmental anomaly.

Senile involution takes place in every body-cell to a certain degree: it appears sometimes earlier in one part, sometimes in another part, of the body. It is due to a primary constitutional chromosomal character of the organism. The special type of general senescence, however, is in a high degree dependent on the special endocrine glands, which are subjected to senile involution in a particular way.

We may distinguish two main types of senile involution. One, the dry, atrophic, emaciating type, shows quite a different general appearance from the second, in which a more or less marked obesity develops, in men usually of the eunuchoid, feminine or asexual kind of fat distribution over the body surface. We may assume in this latter type a predominating senile atrophy of the genital and thyroid glands modifying and molding the general appearance, whereas the first type of general senescence will bring to our mind rather the suggestion of a prevailing senile atrophy of the pituitary gland, when we recall the rather obvious resemblance of these dry, emaciating old people with the so-called pituitary cachexia described for the first time by Simmonds. Anatomical investigations on this subject are being carried out by my collaborators in Vienna at the present time.

I have tried to recall to your memory the importance and high power of the chromosomes and their constituents, to show that the endocrine glands generally are only, as it were, condensers or multipliers of certain chromosomal potencies, and that not everything which may be attributed today to pure endocrine disturbances is, in reality, of endocrine origin. The interference of general chromosomal (i. e., constitutional) and of incretory influences is to be taken into consideration in the greatest number of cases where up to date unsatisfying hypothetical suppositions of pure hormonal trouble usually are to be met with.

A practical consequence I have drawn from these theoretical views may be mentioned, although the experiments have not yet been carried out far enough to be conclusive. If the chromosomes are the primary substratum of the potencies for growth and evolution, then it may be possible to transmit this marvellous high power to an organism whose power is in this respect

deficient. I tried to utilize this power in the maximal degree obtainable from fetal organs, and am now treating in Vienna cases of dwarfism and infantilism with extracts of fetal organs, partly from fetal calves, partly from human fetuses. Up to date these experiments seem to be yielding satisfactory results. I may add that Carrel and his pupils add to their culture media, upon which they grow the different body-tissues in vitro, embryonic extracts as a stimulus.

# PHAGOCYTOSIS IN TOXIC GOITRE

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## I

The presence of scattered lymphocytes and even well-defined lymphoid nodules in exophthalmic or toxic goitre is very well known. Simmonds (1) traced them in about 80 per cent of the cases examined, while Koehler (2), in his classical work, discussed at length their presumed origin and considered them as being attracted in the diseased gland by the alteration of the colloid. Mallory (3) came to similar conclusions and insisted on the phagocytic power of the lymphocytes toward the altered colloid. Quite recently, again, Troell (4) found lymphoid infiltration in 90 per cent of the diffuse, toxic goitres examined by him. However, the existence of marked phagocytosis of the actively working thyroid cells themselves is a fact which seems to have been overlooked.

My purpose is to draw attention to this particular point and to give an accurate description of the different stages of the process by referring to the figures accompanying this paper.

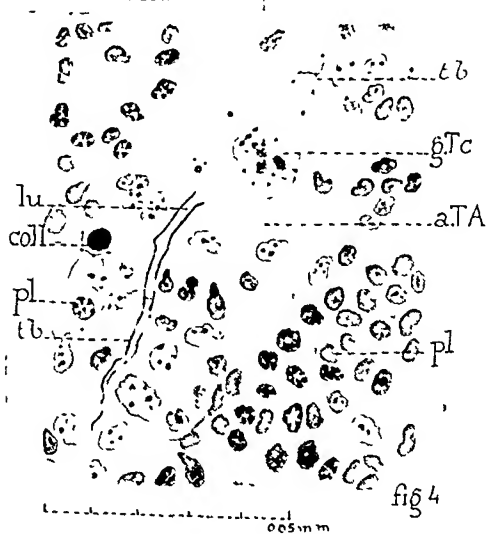
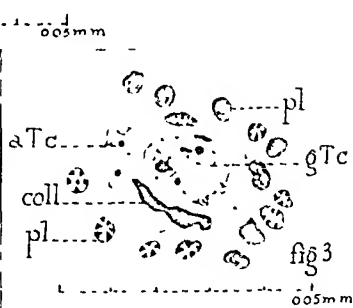
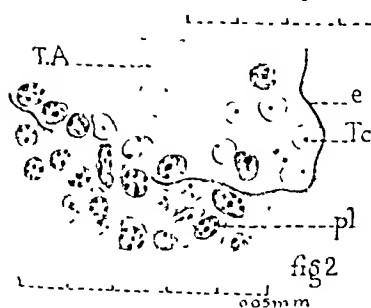
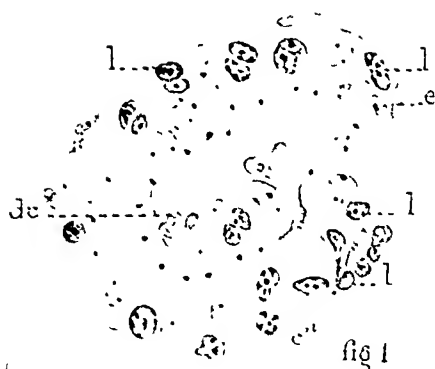
To begin with, small lymphocytes break through the connective framework (c, Fig. 1) surrounding an apparently active secreting thyroid alveolus (l, Fig. 1), and lodge at the bottom of the cells. In Fig. 1 is seen a very striking feature of a lymphocyte (1) with elongated and twisted nucleus disarranging the connections of the glandular cell and repelling the latter into the lumen. Desquamation is—at least in this instance—the result of the invasion of lymphocytes.

When these elements occur in greater number, the connective lining of the vesicle is resorbed at places (Fig. 2). The increase of the phagocytic power of the lymph cells is proved by the fact that they acquire a larger amount of dark, basophil protoplasm and all of the characteristics of the phagocytic plasma cell with its wheel-like nucleus (pl, Fig. 2). The effects of their functional activity can be followed now, step by step.



## ABBREVIATIONS

- 
- a T A altered thyroid alveoli  
a T c, altered thyroid cell  
coll, colloid  
dc desquamated cell.  
c connective frame work  
g T c, giant thyroid nucleus.  
l, lymphocyte  
lu lumen  
pl plasma cell  
T A thyroid alveoli  
tb terminal bus



The protoplasm of the thyroid cell disappears gradually. As a result of this cytolysis, a colorless halo separates the phagocytic from the glandular cell. Very soon also the nucleus of the thyroid cell gives evidence of progressive alteration and it loses its spherical shape; the nuclear membrane becomes wrinkled and in the end disappears altogether. Pycnosis and karyolysis are the final stages (Figs. 3-4). Yet, in these phagocytic acini giant nuclei sometimes exist (g.T.c, Figs. 3-4), but most of them become irregular in shape and poor in a sort of condensed and scattered chromatin (g.T.c, Fig. 4).

These degenerative processes alter deeply the normal architecture of the thyroid vesicle. Cellular limits can no longer be traced and the protoplasm appears as a structureless mass, vacuolized or disintegrated in places (Figs. 3-4). At such an advanced period as is represented in Fig. 4, it would even seem difficult to recognize in these altered elements previously secreting thyroid cells. Yet a careful examination makes clear that such is the case. The most decisive criterion in establishing their identity is the existence of terminal bars (t.b., Fig. 4) which seem to remain present in about 50 per cent of thyrotoxic goitres according to Troell (4). Our preparations show that they resist phagocytosis a long time, and that they prove most useful in identifying the badly damaged thyroid acini. In other instances, the presence among the cells of a small, compact mass of colloid, intensely stained by iron hematoxylin, is another way of ascertaining the thyroid nature of the degenerated cell masses (coll, Fig. 3). However, the presence of this basophil colloid, although very frequent, is by no means constant.

Complete destruction of the thyroid cells is the end of the whole process. Large areas of previously hypertrophic thyroid tissue are now replaced by a diffuse infiltration of lymph cells, among which scattered and altered thyroid elements can be identified here and there. It now remains to show in what pathological variety of goitre the transformations described above can be seen, and then to analyze what kind of thyroid cells undergoes phagocytosis.

## II

The amount of material in which I discovered the alterations referred to is very small indeed. It consists of two speci-

mens of toxic goitre—the only two I have had opportunity to examine since I took the direction of the department quite recently. Still, the facts are conclusive enough to be published and the data given here may be of some use to other investigators working on a more extensive scale. Figs. 1 and 2 belong to a clinically true exophthalmic goitre in a woman forty-five years of age, operated on a year and a half after the onset of the symptoms. Ligation of the arteries was performed previous to thyroidectomy. The pathological aspect of the goitre is of the type which Wilson (5) would classify as an advanced primary hypertrophic and hyperplastic goitre. In fact, it corresponds to the classical image reproduced in our modern textbooks [vide Mallory (3), MacCallum (6), P. Masson (7)].

Big lymph nodules are present. Yet I want to draw attention to two particular features: degenerative changes of the thyroid vesicles without any sign of phagocytosis can be traced, but very seldom; there are, on the average, one or two acini every ten sections of one square inch surface. They are quite different from any of the acini shown in our drawings. On the other hand, close to the big vessels exist lumenless tubules of the embryonic type. We consider them as composed of reserve cells to be compared, for instance, to those of the glomerular zone of the suprarenal cortex. They turn gradually into large, secreting cells.

Figs. 3 and 4 have been drawn from a diffuse (exophthalmic?) toxic goitre in a woman forty years old. The disease began after recovery from influenza about a year ago. Rest-cure and Moebius serum greatly improved the patient's condition, according to the surgeons' report. However, relapse occurred six months later; thyroidectomy was performed without any previous ligation of the arteries. I could not ascertain that this case corresponds to the accurate conception of true exophthalmic goitre emphasized by Plummer (8) and Wilson (5). I do not know whether the required tests have been performed, yet we can certainly consider it as a severe toxic goitre.

On section, the removed gland looks pink, but shows here and there colloid nodules about 0.5 cm. in diameter. Microscopically, this diffuse goitre is composed of fairly regular-shaped acini—spherical or ovoidal—the size of which offers great

variations. The striking features of this goitre are the complete absence of foldings of the epithelium or papillary projections into the lumen, the larger dimensions and the cubical rather than columnar shape of the cells and the presence of a thick basophil colloid in a great number of the alveoli. Mitochondria are extremely abundant in some of the acini. Mitotic figures can be detected. In strong contrast with those active zones appear, in sections, the circular areas of colloid regression with their distended acini and flattened epithelium.

### III

The question arises as to what kind of thyroid cells undergoes phagocytosis. First let us remark that the existence of a phagocytic process has nothing to do with the previous ligation of arteries. In fact, it is more pronounced in the goitre where no preliminary tying of vessels was performed.

On the other hand, the thyroid acini showing types of regression such as described, for instance, by Ribbert (9), are, generally speaking, not affected by the phagocytic process. The same is true of the colloid areas.

Lymphoid infiltration is most marked in the neighborhood of big vessels and just there are located the small and least differentiated thyroid cells, tubules or acini. The lymph or plasma cells attack especially those small acini that are just turning from the tubular into the alveolar form. Yet, middle-sized, spheroidal acini, provided with high epithelium, can undergo the same process, but never to the same extent or frequency.

Newly differentiated acini show every sign of functional activity. In both goitres examined they give most striking evidence of richness in granular or ring-like mitochondria derived from the rod-like ones of the resting period. Big nuclei, turgescient but quite regular and double the average diameter, can be seen inside and on the border line of areas where phagocytosis takes place. That this enlargement of nuclei is not a pathological consequence of the dense lymphoid infiltration seems proved by the fact that these nuclei are found sometimes—though in much smaller numbers—in non-infiltrated areas. These nuclear and protoplasmic peculiarities show that phagocytosed areas are composed of very active thyroid cells.

However, hyperfunction of the glandular cells is not the only reason for attraction of the lymph cells, since it is evident that the larger, hyperplastic acini provided with papillary projections into the lumen and also very active, do not undergo phagocytosis at all. Qualitative influences must intervene of which we have, unfortunately, but little objective data. Small acini with basophil colloid are attacked as well as those containing a more fluid secretion stained by eosin or light green. The reaction of the colloid with Azocarmin (Mallory) and its relationship with phagocytosis has not been investigated. This would seem to be a promising field for research, in view of the data given by Troell (4) concerning discrimination of the thyroid secretion. It is concluded that *only those thyroid acini undergo phagocytosis which are newly differentiated and are at a special stage of functional overactivity.*

Is phagocytosis a constant phenomenon in exophthalmic or toxic goitre? This question can be answered better by those to whom more abundant material is available. Now that attention has been called to the process, it is possible, for instance, that, judging by Goetsch's (10) microphotographs, it will be easily detected in goitres which that author calls "diffuse adenomatosis."

It is not our intention to dwell on the biological significance of phagocytosis in toxic goitre. Evidently it is a defensive process which may be, perhaps, compared with Murphy's (11) and Rubens Duval's (12) lymphoid reaction in tumors. The chemical nature and the toxicity of the cell-metabolism products are probably the underlying causes of the phenomena described here. Our findings seem to indicate that these observations give support to the dysthyroidism theory of exophthalmic goitre, but it would be unwise to draw such a general conclusion from the small amount of material here investigated.

#### SUMMARY

1. Besides the well-known lymphoid infiltration in toxic and exophthalmic goitre, there is a marked phagocytosis of thyroid cells. The different stages of the process are described.
2. Phagocytosis is seen in toxic goitres of different pathological aspects, both in the one showing so-called primary hyper-

trophy and in another showing, besides active lobes, degenerative colloid areas.

3. Only those thyroid acini undergo phagocytosis that are newly differentiated and give evidence of great functional activity.

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# SOME FAVORABLE EFFECTS FROM THE ALIMENTARY ADMINISTRATION OF INSULIN\*

(Preliminary Communication)

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The desirability of finding a satisfactory method for oral administration of insulin requires no argument. In July, 1922, some observations (1, 2) on the absorption of the hormone after the instillation of a crude extract into the human duodenum were made. But the method is obviously impracticable as a routine practice in the treatment of diabetes. Since that time we have tried several other methods. Many of our attempts failed altogether, some were quite equivocal in their results, and a few were apparently so clearly positive that they should be placed on record even though the experiments at this time are incomplete.

Insulin is rapidly destroyed by pepsin (3, 4) if given sufficient time in the stomach or if not protected in some way against its action. It is also rapidly destroyed or inactivated in tryptic digestion (3, 5). Both of these results have been repeatedly confirmed in this laboratory. The problem, then, is to find a means of circumventing these destructive agents. In duodenal administration only one of these agents needs to be evaded and this apparently was accomplished in our observations by the simple expedient of leaving the extract acid with hydrochloric to the extent of from 0.1 to 0.2 per cent. Alcohol also was added with the idea of increasing the chances of absorption.

Another possible means of defeating or escaping the destructive action of pepsin seemed to be the administration of large volumes of slightly acidified extract in the hope that some of it would be evacuated from the stomach before pepsin had a chance

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to diffuse throughout the solution. This was tried up to the limit of 3 liters of the extract daily. It was given as a broth both hot and cold. Some of the broth was sent also to several of the larger clinics. The results were nearly uniformly negative.

Next, in the hope that a still more concentrated solution than our first filtrate might be efficacious, the insulin was precipitated together with some protein by our usual method of saturation with sodium chloride (6), and the precipitate taken up in a much smaller volume of acidulated water. This gave positive results on both partially and totally depancreatized dogs (Table 2), showing that it had passed the stomach successfully. It was then tried on several human subjects with, at first, encouraging results (7). Examination of the same patients after a somewhat longer period, however, showed that the alimentary tract had apparently adapted itself to the higher concentration and succeeded in destroying the hormone. Chart I illustrates the successive increases in dosage which were necessary to produce a lowering of blood and urine sugar.

Even before this, desiccated material obtained by acetone precipitation of insulin from crude extract and drying was tried, but with disappointing results.

We then tried alcoholic solutions by stomach, and although positive evidence of absorption, both in the normal rabbit and in partially depancreatized dogs, could be obtained in agreement with Winter (8), the results with human patients to date have not been satisfactory. This is confirmed by Salèn (9).

Finally enteric coated capsules and tablets were tried. Small gelatin capsules were filled with dried insulin material obtained from our salt precipitate, and were coated over with salol. The salol coated capsule was enclosed in a larger gelatin capsule. After several trials with dogs and patients it was found that the salol coating disintegrated often in artificial gastric juice and sometimes withstood artificial tryptic digestion for several hours. In a few instances, however, notwithstanding these results in artificial digestion, the salol coating seemed to accomplish the result *when the capsule contained in addition to insulin a harmless substance calculated to delay the action of trypsin temporarily in the immediate neighborhood of the capsule when it went to pieces in the intestine.*

This method was then improved by having more perfect enteric coatings prepared for us by reputable pharmaceutical manufacturers and it is this form of tablet which has encouraged us to make a preliminary report of some favorable results of enteric administration of insulin.

The exact methods of enteric coating are unknown to us; but in artificial gastric juice the shell withstands digestion for

TABLE 1.  
TESTS ON HUMAN SUBJECTS.

Patient	Date	Amount and No. of Extract	Drop in Blood Sugar (mgm)	Hours	Drop in Urine Sugar in 24 Hours (gms)	Remarks
Bu <sup>1</sup>	1922	DUODENAL ADMINISTRATION First blood before breakfast.				
	July 6-7	360 cc. No. 25 (2) + 0 1% HCl	61	11	22	
	8-9	400 cc. No. 33 + 0 2% HCl	40	2½	20	
	15-16	250 cc. No. 39 (1) + 0 1% HCl	40	2	34	Following 250 cc 0 3% Na <sub>2</sub> CO <sub>3</sub> .
	18-19	500 cc. No. 41 (2) with 6% alcohol	60	4	8	
	20-21	1000 cc. No. 49 (1) with 6% alcohol	60	4½	34	2 doses 3½ hours apart.
Bl	18-19	500 cc. No. 45 (2) with 8% alcohol	101	6	16	Patient intoxicated A. M.
	22-23	500 cc. 5% alcohol.	36	3	7	
		500 cc. No. 48 (2) with 5% alcohol	42	5½	13	P. M.
	25-26	700 cc. No. 46 (1) with 5% alcohol	53	8½	6	
	27-28		34	8½	1 1	
	29-30		42	9½	5 0	
E. V.	1923	Sugar excretion 24 hrs. gms.				
	Nov. 8	30 units insulin subcut. and 6 tablets daily.	50		Sugar free	
	9	30 units insulin alone.	142		Sugar free	
E. M.	1924					
	Jan. 7-12	6 to 12 tablets daily, Jan 7	500		61 6	Both blood and urine had been on increase previous to use of tablets.
		Steady drop to Jan 12	265		13 7	
	15-19	16 tablets daily, Jan 15	344		42 7	
		Steady drop to Jan. 19	303		19 8	

<sup>1</sup>This case is reported from Highland Hospital by the courtesy of Dr. John R. Williams

at least three hours and opens up within 15 to 30 minutes in artificial tryptic digestion.

For delaying temporarily the action of trypsin and thus affording an opportunity for the absorption of insulin we fol-

lowed the hint obtained from direct duodenal administration, namely, of introducing with the insulin material weakly acid substances in varying proportions. Several weak organic acids which naturally occur to one for this purpose are: citric, malic, tartaric acids, etcetera, and weakly acid salts such as sodium dihydrogen phosphate. All of these have been tried with, as yet, no clear advantage of one over the others.

Table 1 presents a few positive tests on human subjects: (1) of duodenal administration and (2) of administration of enteric coated tablets containing acid substances.

The efficacy of duodenal administration can scarcely be doubted; for in addition to evidence of effects upon blood sugar and urinary excretion of sugar, the patients, both being cases of severe type, experienced improvement in clinical appearance and muscular strength and showed some gain in weight. With alcohol there was a little greater effect on the blood sugar though scarcely upon excretion, and there was some effect on both with alcohol alone (10). The four tests with extract alone in weak acid prove, we think, that insulin can be absorbed from the human gut without the aid of alcohol. That the acid alone could not have caused the effects either directly or through delay of intestinal digestion is strongly indicated by the fact that even small doses of hydrochloric acid increase the output of sugar and depress the respiratory quotient in depancreatized dogs (11). Haemaglobin tests with patient B1 showed that the effect on blood sugar could not have been due to dilution.

With regard to case E. K., shown in Chart 1 but not in the table, it should be explained that the boy was purposely placed upon a diet somewhat above his tolerance because his parents were very desirous that he should gain weight rapidly during the summer months so that he could enter school in the fall. During the period of observation in the hospital, represented by the chart, he was on a constant diet, and the sugar in both blood and urine was increasing from day to day before administration of the broth was started. The very first dose containing 72 rabbit units produced a satisfactory reduction in both, but this amount soon became ineffective. Only when resort was had to the salt precipitate and the dosage increased to 300 rabbit units was the next reduction accomplished. When the second day at this level showed no further improvement the dose was

increased to 600. Again a reduction occurred the first day, but did not persist the second. Broth in the original dosage was then tried, but was wholly ineffective. Salt precipitate in amounts up to 800 rabbit units later did not produce so great an effect as originally had been produced by much smaller doses.

E.K. Aet. 13

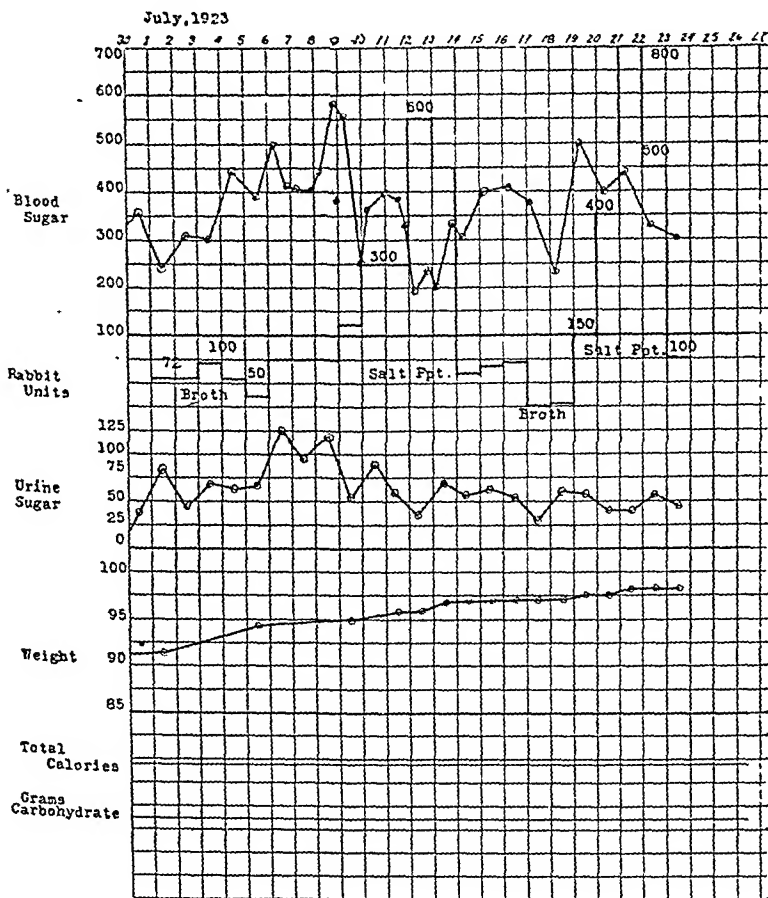


Chart 1. Case E. K., age 13. Showing increasing dosage of salt precipitate necessary to produce effects on blood sugar and urine sugar.

There seems, then, to be evidence in this chart of rapid adaptation in the secretory mechanisms of the alimentary tract to meet the exigencies presented by such material.

The boy's weight gradually increased throughout the period because his tolerance was sufficient to handle the necessary

caloric intake, and he suffered no harmful effects so far as could be noted. The experiments with stomach administration were stopped as soon as it was clear that his tolerance could not be substantially improved by this method.

The first enteric coated tablets containing insulin and organic acids were used with human patients in July, 1923. Two such subjects not in the hospital were rendered sugar free, but because we cannot vouch for the constancy of the diets claimed by them no scientific report of the cases can be made. Two others shown in Table 1 gave reactions which are not to be doubted. The first, E. V., was a severe case which required 30 clinical units of insulin subcutaneously to keep the urine free of sugar. Six tablets were added with the idea of replacing a part of the subcutaneous dosage. The blood sugar, however, went so low (it remained at near 50 milligrams, "fasting," for three days) that the tablets were withdrawn; whereupon the blood sugar next day rose, without change in the subcutaneous dosage, or change in the diet, to 142 milligrams. The patient left the hospital a few days later before it was possible to repeat the test.

The other patient, E. M., a boy of 13, had been in the hospital on a constant diet for six days before the tablets were started. During this time the blood sugar gradually rose from 275 milligrams to 500 and the urine from 38.5 to 61.6 grams. With from 6 to 14 tablets daily, taken in lots of two to four, one-half hour before meals the sugar began at once to fall and continued steadily to do so until the levels shown in the table for January 12 were reached. At this point, in spite of an increase to 16 tablets, the sugars began to rise and continued so to do for three days. For the following four days the tablets were taken by the boy while lying on his right side and sipping water for 15 minutes to one-half hour before meals. This technique which is well known to be effective for passing the duodenal tube seemed to be effective also in securing prompt passage of the tablets into the duodenum. At all events the decline in both blood sugar and urine sugar was continuous to the levels indicated in the table for January 19. Increasing the tablets to 32 per day did not have any further effect, possibly because they contained sufficient carbohydrate to offset the favorable effect of the insulin. These particular tablets were coated

with milk sugar and contained also a small amount of starch necessary for compacting the material. The boy left the hospital and although he has received since that time other tablets of the same general nature which seemed to act favorably no accurate report of the effect can be made.

## TESTS ON DIABETIC DOGS

In Table 2 are given a few favorable effects upon depancreatized dogs. All these animals had been under observation and control as regards diet for at least two weeks following

TABLE 2.  
TESTS ON DEPANCREATIZED DOGS.

Dog No.	Date 1923	Amount of Extract	Drop in Blood Sugar (mgms)	Hours	D N	R Q	Urine Sugar (gms)	Remarks
47 Partial	June 28	9:35 A.M. 450 cc. No. 11, broth.	32	5				Dog fed meat diet every day same.
	29	10:10 same.						
	30	900 cc. No. 17 broth	17	6	2 52			
	July 10	100 R. U. salt ppt. No. 17	(212)		1 86			
	11	100 R. U. salt ppt. in sol.	47 (165) 11 (150)	24 24	2 28 2 34 0 0		Sugar free	
54 Partial	Oct. 8	4 enteric capsules	32	5½			10 10	Food same.
	9						1 09	10/6 to 10/10
	18 19	3 enteric capsules	63	24	1 90 1 00			Food same. 10/15 to 10/20
51 Total; two weeks after operation	June 27	200 R. U. No. 16 salt ppt. in sol.			2 70	0 699 0 709	5 03	Food constant..
	June 28	200 R. U. No. 16 salt ppt 40 gm. glucose				0 829 0 765 0 781 0 885 0 825 0 721	11 18	
	June 29	20 gm. glucose.				0 951 0 958 0 898	15 84	
				Alcohol	check	0 647 0 647		
	June 30	20 gm. glucose.				0 801 0 816 0 800	Sugar free	

operation before the experiments here reported were made. The "broths" used with dog No. 47 were obtained by simple aqueous extraction and contained at the time of administration only a small amount of HCl (pH 4.0). The fall in blood sugar is not great, but taken in conjunction with the decline in the

D:N while the diet remained constant, it can be regarded only as a positive effect of insulin; for the dog was fed only in the evening after the observations on the blood had been completed. In order to increase the dose of insulin without increasing the volume intake of fluid, the insulin was precipitated together with some protein from the aqueous extract and the precipitate containing some 100 rabbit units was dissolved in 200 cc. of water. The first dose produced a fall of 47 milligrams in the morning blood sugar for 24 hours but did not reduce the D:N ratio. In fact, both the sugar and nitrogen were increased on account of the protein contained in the salt precipitate. The next day, however, the blood sugar taken at the same hour was still lower and the urine was entirely sugar free. The effect could not have been due to any injurious effect of salt contained in the salt precipitate, for its amount was very small. Nor could it have been due to any tendency of the pancreatic fragment to resume its function; for the diabetes became steadily worse, and later could not be controlled by stomach administration of salt precipitate. Twice after this the urine became sugar free, but the effect was not so clear cut as in this instance.

With dog No. 54 the enteric capsules, containing dried salt precipitate and a substance designed to delay tryptic destruction of insulin, similar in composition to the tablets employed with the human subjects were used. In the first test four such capsules lowered the blood sugar 32 milligrams in 5½ hours and produced a drop in urinary excretion of sugar for the 24 hours of 9 grams. In the second test the drop in blood sugar was 63 milligrams for 24 hours. The D:N ratio is only approximately correct.

The most conclusive proof of absorption of insulin was obtained with the totally depancreatized dog No. 51. The dog was certainly diabetic as proved by the high blood sugar, the Minkowski D:N ratio on a meat diet two weeks after pancreatectomy and the perfectly typical diabetic respiratory quotient. Two doses of the salt precipitate in water amounting to 200 rabbit units each, one on the 27th and the other on the 28th, followed by 40 grams glucose by stomach tube, produced within a few hours after glucose respiratory quotients well above the diabetic level, and a utilization, assuming the same D:N ratio, of nearly thirty grams of glucose in 24 hours. The

D:N ratio could not be accurately determined because of the unknown amount of protein in the salt precipitate. The next day the quotient went even higher after glucose and the following morning the urine was sugar free in spite of the 20 grams glucose given. An alcohol check experiment on the 30th proved that the apparatus was working properly, and the dog's R. Q. after a third dose of glucose indicated continued combustion. The dog of course had no pancreatic juice, hence the insulin was not destroyed by trypsin. There was at no time any sign of overdosage of insulin, due, no doubt, to its excretion through the urine (12).

#### CONCLUSIONS

The observations here reported prove, we think: (1) that insulin in crude solution containing 0.1 per cent HCl, placed directly in the duodenum of the diabetic patient, can be absorbed and can function to cause the utilization of sugar; (2) that insulin placed in enteric coated tablets containing a substance designed to delay temporarily the destructive action of trypsin can survive the stomach in some patients, can be absorbed in the intestine, and can operate to improve the diabetic condition very materially.

The practicability of these methods of administration cannot be vouched for in all cases, but it would seem that in many cases they might be used at least to relieve the tedium of frequent hypodermic injections of more refined products.

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# BLOOD PRESSURE AND SUGAR METABOLISM

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## BLOOD CONSTITUENTS IN HYPERTENSION

The facts definitely known about genuine hypertension are few in number. It is even a problem whether this form of hypertension represents a clinical picture. Peters, who studied the kidney function in cases of genuine hypertension, always found symptoms of a disturbed function of the kidney. Since, however, the work of Peters has not always been confirmed, I take the genuine hypertension as an existing clinical picture. This disease is of the greatest importance for the endocrinologist; it raises especially the two problems: (a) is there a normal sugar metabolism in hypertension; (b) may the hypertension be attributed to hyperfunction of the chromaffine system?

As far as I know, Neubauer (1) was the first to study sugar metabolism in cases of high blood pressure. He stated that in these cases (his patients all suffered from Bright's disease) there existed hyperglycemia. His work was confirmed by Hirsch (2), Tachau (3) and Hagelberg (4). Hitzengerber and Richter-Quittner (5) determined the blood sugar in cases of essential hypertension and found it also increased. Nevertheless, the statement that high blood pressure and high blood sugar consistently occur together has been denied repeatedly. Stilling (6), Frank (7) and Kahler (8) are among those who were not able to confirm the work of Neubauer. Riesman (9) found thyrotoxic symptoms in many patients with hypertension. He does not give reports of blood sugar estimations, but in thyroid toxicosis blood sugar generally is high.

According to Hovens Greve (10) cases of hypertension may also show hyperglycemia. This relation, according to this author, is not at all constant. Harrower (11) described symptoms of latent myxedema in hypertension. I do not believe, however, that any other investigator agrees with this statement. Mention should be made also of an article by Fahr (12).

Hitzenberger and Richter-Quittner attribute hyperglycemia as well as hypertension to hyperadrenalinemia. Fahr, however, bases his theory on the fact, well known to all pathologists, that the blood vessels of the pancreas often suffer from sclerosis. He believes that this sclerosis causes a diminished secretion of the pancreas hormone and in this way is responsible for a hyperglycemia. Fahr also claims that there exists an antagonism between the pancreas and the adrenals. In this way a secondary hyperadrenalinemia may accompany the hyperfunction of the pancreas. Fahr's opinion is well conceived but it is based on numerous unproved statements. These quotations, though not complete, proved how little is known about the relations between blood sugar and vascular tension.

In my own studies in fifty patients with hypertension the blood sugar was measured on the empty stomach with Bang's micromethod. Thirty of these patients were tested for alimentary glycosuria with 100 gm. glucose. Ten patients took for three days a diet poor in purin substances. On the fourth day the uric acid content of the blood was determined on the empty stomach with Autenrieth's colorimeter.

	Age, Sex	Blood Pressure Riva Rocci	Blood Sugar Bang	Alimentary Glycosuria	Uric Acid mgr. /100 cc.
1	63 m.	210-240	0.12	—	2.8 mgr.
2	41 fem.	220-250	0.19	—	1.4
3	52 fem.	170-195	0.17	—	1.2
4	73 fem.	200-240	0.22	—	2.4
5	42 m.	160-220	0.09	—	2.1
6	80 m.	145-175	0.09	—	4.1 !!
7	49 fem.	180-230	0.13	+	1.5
8	70 fem.	180-215	0.16	—	2.0
9*	68 fem.	170-200	0.24	—	1.4 diabetes
10	56 fem.	180-230	0.14	+	3.5
11	63 m.	150-170	0.12	—	
12	60 fem.	135-170	0.08	—	
13	49 fem.	210-240	0.13	—	
14	59 m.	190-220	0.11	—	
15	68 fem.	155-185	0.10	—	
16	71 m.	230-265	0.12	—	
17	56 m.	230-245	0.09	—	
18	54 m.	165-180	0.10	—	
19	70 m.	265-300	0.12	—	
20	38 m.	160-210	0.14	—	
21	60 fem.	185-215	0.14	—	
22	46 m.	160-200	0.14	—	
23	68 m.	185-205	0.13	—	
24	61 fem.	210-230	0.09	+	
25	53 m.	240-270	0.15	—	
26	70 m.	140-170	0.24	—	
27	68 m.	200-225	0.17	+	
28	60 m.	175-195	0.09	—	

29	41 fem.	180-195	0.13	—
30	56 fem.	205-215	0.16	—
31	63 m.	225-235	0.20	
32	65 fem.	210-240	0.14	
33	64 m.	205-230	0.22	
34	76 m.	170-190	0.11	
35	44 fem.	200-220	0.15	
36	51 m.	230-260	0.20	
37	46 m.	205-220	0.12	
38	59 fem.	165-180	0.16	
39	70 fem.	160-195	0.10	
40	80 fem.	185-210	0.15	
41	46 fem.	230-260	0.08	
42	58 m.	150-185	0.14	
43	56 m.	200-235	0.17	
44	53 m.	210-245	0.12	
45	68 m.	160-210	0.21	
46	61 fem.	170-195	0.13	
47	64 m.	140-185	0.17	
48	42 fem.	210-245	0.18	
49	79 m.	160-175	0.23	
50	69 fem.	180-210	0.10	

\*Patient 9 complained of thirst and furunculosis. She had no glycosuria; perhaps she suffered from a beginning or latent diabetes as described by Marañon.

The data of this table indicate that hyperglycemia in hypertension is exceptional, as are augmented uric acid in the blood and alimentary glycosuria.

#### BLOOD PRESSURE IN DIABETES

It is an important problem whether the blood pressure in diabetes is normal. The question has been raised repeatedly in medical literature. Hitzenger (13) states that in young patients with diabetes the blood pressure is, as a rule, somewhat lower than in normal individuals of the same age. Elderly patients with diabetes have, according to this author, high blood pressure. Kylin (14, 15) on the contrary finds in young diabetics a perfectly normal blood pressure, in elderly patients a high one. According to Kylin, diabetes with hypertonia is quite another endocrine disease than diabetes with normal blood pressure. He firmly denies that in hypertonia there always is hyperglycemia, though he believes that there is an unknown relation between diabetes and hypertonia. He quotes experiments (injections of adrenalin) which sought to prove the endocrine cause of hypertonia. The problem is discussed in quite another way by Marañon (16). He often finds a high blood pressure before the detection of glycosuria. As soon as symptoms of real diabetes develop, the high blood pressure sinks. When a

person of about 40 has hypertension with, or even without, hyperglycemia he is inclined to become diabetic, especially when he suffers from adiposity. Marañon describes a pre-diabetic stage in which the patients complain of itching, neuralgia, furunculosis, etc. Rosenbloom (17) studied the blood pressure in 140 cases of diabetes. He found in ordinary uncomplicated diabetes a normal or a slightly decreased blood pressure. Hypertonia was found only when complications such as aortitis, nephritis, arterio-sclerosis or heart diseases were present. In acidosis blood pressure was generally low.

I measured the blood pressure in 161 cases of diabetes. Among these were:

- A. 3 patients under 10 years.
- B. 7 patients from 10-20 years.
- C. 30 patients from 20-30 years.
- D. 41 patients from 30-40 years.
- E. 36 patients from 40-50 years.
- F. 41 patients from 50-60 years.
- G. 3 patients over 60 years.

A.

Age, Sex	Urine	Blood Sugar	Complications	Blood Pressure
7 years	Gluc., acet., diac. acid	0.23		80-94
7 years fem.	Glucose	0.28		76-100
9 years fem.	Glucose, acetone	0.24	t. b. c. left apex	92-140

B.

Age, Sex	Urine	Blood Sugar	Complications	Blood Pressure
11 years fem.	Gluc., acet., diac. acid	0.22		100-125
12 years m.	Glucose, acetone	0.21		95-110
15 years fem.	Acetone, diac. acid	0.36	t. b. c. pulmonum	110-135
15 years fem.	Gluc., acet., diac. acid	0.24		90-105
17 years m.	Gluc., acet., diac. acid	0.19		85-105
18 years m.	Glucose	0.23	Br. disease, edema	130-165
18 years fem.	Gluc., acet., diac. acid	0.30		100-120

C.

Age, Sex	Urine	Blood Sugar	Complications	Blood Pressure
21 years m.	Gluc., acet., diac. acid	0.19		95-120
21 years m.	Glucose, acetone	0.23		90-120
21 years m.	Gluc., acet., diac. acid	0.24		85-130
23 years fem.	Glucose	0.31		100-130
23 years fem.	Glucose	0.18		110-130
23 years m.	Acetone, diac. acid.	0.20		115-140
23 years m.	Glucose	0.37		105-115
23 years fem.	Glucose	0.28		95-125
23 years m.	Gluc., acet., diac. acid	0.30	Psoriasis	80-100
23 years m.	Glucose, acetone	0.25		90-125

24 years m.	Glucose, acetone	0.20		85-100
24 years m.	Gluc., acet., diac. acid	0.34		120-135
24 years m.	Glucose	0.30	Furunculosis	120-140
24 years fem.	Glucose	0.28		100-135
24 years fem.	Glucose, acetone	0.21		80-95
25 years m.	Glucose	0.31		110-145
26 years fem.	Gluc., acet., diac. acid	0.19	Dysenteria	105-145
26 years fem.	Glucose, acetone	0.23		85-100
26 years fem.	Gluc., acet., diac. acid	0.34		105-140
26 years fem.	Glucose	0.21		95-105
26 years fem.	Glucose	0.28	Ulcus ventriculi	100-120
26 years fem.	Glucose	0.34		100-145
26 years fem.	Gluc., acet., diac. acid	0.30	Ulcus ventriculi	90-105
26 years m.	Acetone, diac. acid	0.21		80-100
28 years m.	Acetone, diac. acid	0.18		95-110
28 years m.	Gluc., acet., diac. acid	0.26		120-145
28 years m.	Glucose	0.31		115-125
30 years m.	Glucose	0.34	t. b. c. pulmonum	80-115
30 years m.	Acetone, diac. acid	0.46		100-125
30 years fem.	Glucose	0.20	t. b. c. pulmonum	95-135

Age, Sex	Urine	Blood Sugar	Complications	Blood Pressure
31 years fem.	Glucose	0.30		90-140
31 years fem.	Glucose	0.21	t. b. c. pulmonum	120-135
31 years fem.	Gluc., acet., diac. acid	0.36		85-120
31 years fem.	Acetone	0.19		90-110
31 years m.	Glucose, acetone	0.32	Ulcus ventriculi	115-140
32 years fem.	Glucose, acetone	0.27		100-135
32 years fem.	Gluc., acet., diac. acid	0.40		80-120
32 years m.	Glucose	0.23		120-145
32 years m.	Glucose	0.21	Ulcus duodeni	75-100
32 years fem.	Gluc., acet., diac. acid	0.25		105-120
32 years fem.	Acetone	0.14		140-165
32 years m.	Acetone, diac. acid	0.12		105-130
32 years fem.	Acetone	0.19		95-140
32 years fem.	Glucose	0.31		85-125
32 years m.	Glucose	0.24		70-100
32 years m.	Glucose	0.30	Syphilis III	95-110
32 years m.	Gluc., acet., diac. acid	0.25		105-120
33 years fem.	Glucose, acetone	0.29		95-130
33 years fem.	Acetone	0.20		110-140
34 years m.	Glucose	0.27	Psoriasis	95-110
34 years fem.	Glucose	0.26		90-125
34 years fem.	Acetone, diac. acid	0.19		75-110
34 years fem.	Gluc., acet., diac. acid	0.24		120-160
34 years fem.	Glucose	0.30		85-110
34 years m.	Acetone	0.20		100-125
34 years fem.	Glucose	0.40		100-110
34 years m.	Glucose	0.39		85-100
35 years fem.	Glucose	0.32	Ulcus ventriculi	90-130
36 years m.	Acetone	0.09		80-100
37 years fem.	Acetone, diac. acid	0.12		105-140
37 years m.	Gluc., acet., diac. acid	0.19		100-140
37 years m.	Glucose, acetone	0.26		85-140
37 years m.	Glucose	0.29		90-110
37 years m.	Acetone, diac. acid	0.18		75-100
38 years m.	Acetone, diac. acid	0.26		120-145
38 years fem.	Gluc., acet., diac. acid	0.33	Caries vertebrae	80-110

38 years m.	Glucose	0.28		95-120
38 years fem.	Acetone	0.19		100-135
38 years fem.	Acetone, diac. acid	0.21		105-140
39 years fem.	Gluc., acet., diac. acid	0.43	Cardiospasm	90-120
40 years fem.	Gluc., acet., diac. acid	0.35		125-140

E.

Age, Sex	Urine	Blood Sugar	Complications	Blood Pressure
42 years m.	Acetone	0.22		120-165
42 years m.	Glucose, acetone	0.26		140-180
42 years m.	Glucose	0.30		130-165
42 years fem.	Glucose	0.24	Menopause	95-140
42 years fem.	Glucose	0.21		160-200
42 years fem.	Gluc., acet., diac. acid	0.29	t. b. c. pulmonum	85-140
42 years m.	Acetone	0.19	Insuf. mitralis	95-120
43 years m.	Glucose	0.20		160-200
44 years m.	Glucose	0.23		120-145
44 years fem.	Glucose	0.31		130-160
44 years fem.	Glucose, acetone	0.30		95-140
44 years fem.	Glucose	0.27	Nephritis chronica	220-265
44 years fem.	Acetone, diac. acid	0.20		160-185
45 years fem.	Glucose	0.30		140-160
46 years m.	Gluc., acet., diac. acid	0.36		155-185
46 years m.	Glucose	0.24		170-205
46 years m.	Glucose	0.27		165-190
46 years fem.	Glucose	0.21	Menopause	110-140
46 years fem.	Glucose	0.35		105-145
46 years fem.	Glucose	0.21		170-205
47 years m.	Glucose, acetone	0.33	Ulcus ventriculi	105-140
47 years fem.	Acetone, diac. acid	0.40	Graves' disease	170-220
47 years m.	Glucose, acetone	0.22		180-210
48 years m.	Glucose, acetone	0.28		155-185
48 years m.	Glucose	0.24		195-240
48 years m.	Glucose	0.30		160-185
48 years m.	Glucose	0.33		150-165
49 years m.	Gluc., acet., diac. acid	0.21		190-205
49 years fem.	Glucose	0.19		170-215
50 years m.	Glucose	0.17		160-200
50 years m.	Diacetic acid	0.24	t. b. c. pulmonum	90-135
50 years fem.	Glucose	0.21		160-210
50 years fem.	Acetone, diac. acid	0.14		200-235
50 years fem.	Glucose, acetone	0.25		160-205
50 years fem.	Glucose	0.28	Cholelithiasis	100-135
50 years m.	Glucose	0.34		190-235

F.

Age, Sex	Urine	Blood Sugar	Complications	Blood Pressure
52 years m.	Glucose	0.30		160-185
52 years m.	Glucose	0.21	Ulcus ventriculi	170-185
52 years m.	Glucose	0.26		140-180
52 years m.	Glucose	0.24		110-165
52 years fem.	Glucose, acetone	0.19		190-215
52 years fem.	Glucose	0.18		145-170
52 years fem.	Acetone	0.14	Emphysema-pulm.	185-205
52 years fem.	Gluc., acet., diac. acid	0.35		160-190
53 years m.	Glucose	0.26		155-180
53 years fem.	Glucose	0.24		100-145
53 years fem.	Glucose, acetone	0.31	Cholelithiasis	170-240
54 years fem.	Glucose	0.24		145-160

55 years m.	Glucose, acetone	0.31		140-170
55 years m.	Acetone	0.20		105-120
56 years m.	Acetone, diac. acid	0.20		95-140
56 years m.	Glucose	0.31	Bright's disease	230-255
56 years fem.	Glucose	0.28		160-195
56 years fem.	Glucose	0.25		110-135
56 years m.	Glucose	0.30		135-170
56 years m.	Glucose	0.29		105-125
56 years m.	Acetone	0.19		140-170
56 years m.	Gluc., acet., diac. acid	0.23	Ulcus duodeni	130-170
56 years m.	Glucose	0.18		100-125
56 years m.	Glucose, acetone	0.23		110-155
56 years m.	Glucose	0.26		105-140
56 years fem.	Glucose	0.38	Bright's disease	270-295
56 years fem.	Glucose	0.22		180-195
56 years fem.	Acetone	0.20		140-165
56 years m.	Glucose	0.29		110-135
58 years fem.	Glucose	0.34		145-170
58 years fem.	Glucose	0.37	Bright's disease	200-235
59 years m.	Glucose	0.28		160-185
59 years m.	Acetone	0.12		195-215
59 years m.	Glucose, acetone	0.29		135-160
60 years fem.	Glucose, acetone	0.40	Bright's disease	190-240
60 years fem.	Glucose	0.26		140-180
60 years m.	Acetone	0.13		160-195
60 years m.	Glucose	0.28	Ulcus ventriculi	155-180
60 years m.	Glucose	0.27		140-175
60 years m.	Acetone	0.20		205-230
60 years fem.	Gluc., acet., diac. acid	0.35	Carcinoma recti	95-120

## G.

Age, Sex	Urine	Blood Sugar	Complications	Blood Pressure
68 years fem.	Glucose	0.23	Arteriosclerosis	220-245
72 years fem.	Glucose	0.21	Arteriosclerosis	230-270
74 years fem.	Glucose	0.24	Arteriosclerosis	190-225

*Conclusion:*

In young diabetics blood pressure is normal; in older patients with diabetes, hypertension is the rule. No relation between complication and blood pressure was found (except, of course, Bright's disease and arterio-sclerosis). Acidosis does not cause a diminished blood pressure.

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# PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR THE STUDY OF GOITER.

Bloomington, Ill., January 23, 24, 25, 1924.

Edited by J. D. MOSCHELLE

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## FIRST ANNUAL MEETING OF THE AMERICAN ASSO- CIATION FOR THE STUDY OF GOITER

The first session convened at St. Joseph's Hospital, 7:45 a. m., January 23.

The program committee announced that they felt justified in featuring ethylene anaesthesia at this annual meeting in view of the fact that it is attracting great interest at the present time and it was so satisfactory at the preliminary clinic held December 17.

**OPERATIVE CLINIC:** Held by Dr. E. P. Sloan, assisted by Drs. G. A. Sloan, Herman Wellmerling, J. D. Moschelle, and Geo. Newell. Four patients were operated under nitrous oxide oxygen anaesthesia, administered by Dr. Wm. Young. Four patients were operated upon under ethylene oxygen anaesthesia, administered by Dr. Dennis Rupp, assisted by Mr. P. J. McCurdy of the Safety Oxygen Gas Machine Company. The anaesthesia was featured and comparison of effects of nitrous oxide and ethylene was made. It was obvious that ethylene is more potent than nitrous oxide, that the patients are anaesthetised quicker and recover normal consciousness sooner than after nitrous oxide.

At 11:30 it was announced by the secretary that 215 had registered, and all were urged to join the Society. A recess was taken for lunch.

### AFTERNOON SESSION

At Mennonite Hospital. Operative Clinic: Dr. E. P. Sloan. Four patients were operated on under ethylene. Very satisfactory ethylene anaesthesia.



At 3:30 adjourned to St. Joseph's Hospital, where arrangements had been made for Dr. Andre Crotti of Columbus, Ohio, to hold an operative clinic.

Dr. Crotti operated two patients with large nodular colloid goiters. All present were invited as guests of the Sloan Clinic, to a smoker to be held at the Illinois Hotel at 9:00 p. m.

Wednesday and Thursday the following program was carried out:

JANUARY 24, 1924—MORNING—7:00 A. M.

The meeting was called to order by Dr. E. P. Sloan, president, who introduced the vice-president, Dr. Geo. W. Newell, of Burlington, Wisconsin, and requested him to take the chair and act as presiding officer during the session.

The vice-president introduced Dr. Harlan Hart of Bloomington, Illinois.

Dr. Andre Crotti of Columbus, Ohio, was then introduced and he held a diagnostic clinic. He discussed non-toxic and toxic parenchymatous goiters, non-toxic and toxic diffuse colloid goiters, and non-toxic and toxic nodular colloid goiters, and illustrated each kind with several patients.

Dr. J. L. DeCourcy of Cincinnati, Ohio, was introduced and heard on "*Surgery of the Thyroid.*"

Dr. E. G. Blair of Kansas City, Missouri, discussed "*Secondary Goiter Operations.*" He also reported conclusions from a large series of cases and showed two patients and discussed them.

Dr. Wm. Englebach of St. Louis, Missouri, then conducted a diagnostic clinic on endocrinology, illustrated with lantern slides.

The meeting adjourned at 12:30.

AFTERNOON, 1:30 O'CLOCK

The afternoon meeting was called to order by the vice-president, Dr. Geo. W. Newell, who introduced Dr. Crotti of Columbus, Ohio. Dr. Crotti gave an address on "*The Etiology of Endemic Goiter and Toxic Goiter.*"

Dr. Wayne Babcock of Philadelphia, Pennsylvania.

Address: Dr. E. R. Arn, Dayton, Ohio. "*An Analysis of Types of Goiter with Indications for Treatment.*"

Address: Dr. F. N. Wilson, Ann Arbor, Michigan. "*Cardiac Disturbances in Association with Diseases of the Thyroid Gland.*"

Dr. E. P. Sloan: I want you to see and hear a few words from a man who has accomplished much for scientific medicine. Especially should we in the Middle West be grateful to him. He is the father and mother and also the wet nurse of the great

Tri-State District Medical Association; the association that has had most wonderful four-day programs annually for several years. All honor to the managing-director who has been so largely instrumental in its success. I want to call upon Dr. William B. Peck of Freeport, Illinois.

Dr. William B. Peck, Freeport, Illinois: I believe you are pursuing the right course in the study of goiter. The medical treatment of goiter is apparently making wonderful progress with the careful and judicious use of iodine and other medical treatment. I was in the Koehler Clinic in Berne, Switzerland, when practically every case of goiter was treated by surgical technique and treatment. Today, I understand that 50 per cent of the cases that were formerly treated surgically are now being treated medically. Dr. Sloan has asked me to say a word about the Tri-State Medical Association.

The next annual assembly will be held at Milwaukee, Wisconsin, October 27th, 28th, 29th and 30th. We expect next year to supervise a clinic tour to Canada, British Isles and Paris with side trips to other clinical centers. The tour is supposed to start on the 16th of May, 1925. Clinics in Toronto, Montreal, Liverpool, London, Leeds, Edinburgh, Glasgow, Newcastle-on-the-Tyne, Dublin and Paris will be arranged in advance. These clinics will be conducted by the most eminent members of the profession in these cities. The cost of the trip, including everything except board in Canada and lasting in the neighborhood of seven weeks, will be approximately \$795.00. The reservations are fast filling up, and we would advise the physicians who wish to go to notify us as early as possible.

Address: Dr. Horace M. Brown, Milwaukee, Wisconsin. "*The Biologic Causes of Incompetency.*"

Address: Dr. Arnold Jackson, Madison, Wisconsin. "*The Relation of Basal Metabolic Rate to Diseases of the Thyroid Gland.*"

Address: Dr. F. M. Hagans, Lincoln, Illinois. "*Radium Treatment of Goiter.*"

Banquet at the Illinois Hotel at 7:00 p. m. Dr. E. C. Williams, president McLean County Medical Society, presiding. Dr. Horace M. Brown, Milwaukee, Wisconsin, acted as toastmaster. Dr. L. C. Taylor, president of the Illinois State Medical Society; Dr. I. D. Rawlings, director of Illinois State Board of Health; Dr. W. B. Hight, Des Moines, Iowa; Dr. E. W. Rowe, Lincoln, Nebraska; Dr. Andre Crotti, Columbus, Ohio; Dr. W. B. Peck, manager Tri-State Association; Dr. H. S. Plummer, Rochester, Minnesota; Dr. Wm. Engelbach, St. Louis, Missouri; Dr. Arnold Jackson, Madison, Wisconsin; Dr. Wayne Babcock, Philadelphia, Pennsylvania; Dr. W. T. Scott, Temple, Texas; Dr. E. C. Blair, Kansas City, Missouri; Dr. Wm. King,

Seattle, Washington; Dr. J. L. DeCourcy, Cincinnati, Ohio, responded to toasts. Eighty-eight were in attendance.

JANUARY 25, 1924—MORNING—8:00 O'CLOCK

The meeting was called to order by Dr. Newell.

Address: Dr. Roswell Pettitt, Ottawa, Illinois. "*Incipient Goiter vs. Incipient Tuberculosis.*"

Address: Dr. E. W. Rowe, Lincoln, Nebraska. "*The Roentgen Treatment of Thyrotoxicosis.*"

This paper was followed by discussions by several X-ray and radium men who were present: Dr. Cantrell and Dr. Grote of Bloomington; Dr. Jackson of Madison, Wisconsin; Dr. Goodman and Dr. McGee of Peoria; Dr. Gillette of Toledo, Ohio.

Dr. Wayne Babcock of Philadelphia, Pennsylvania, conducted a diagnostic clinic. This clinic was followed by discussions by Dr. Jackson of Madison, Wisconsin; Dr. Arn of Dayton, Ohio; Dr. Dryer of Aurora, Illinois, and Dr. Moschelle of Indianapolis, Indiana.

Dr. J. W. Turrentine of Washington, D. C., was unable to be present. His paper on "*Use of Scaevd in the Prevention and Treatment of Goiter,*" was read by Dr. Moschelle, the secretary.

Dr. Frank H. Lahey of Boston, Massachusetts, was unable to be present. His paper, "*A Review of Another Year's Work with Thyroid Diseases,*" was read by Dr. Sloan.

It was suggested to the chair that Dr. Kennan Dunham of Cincinnati, Ohio, be on the program at the Chicago meeting, the Tuesday before the A. M. A. meeting.

Dr. Moschelle asked the members to send in questions and answers about perplexing problems so that they may be brought up at the Chicago meeting.

The meeting then adjourned to St. Joseph's Hospital, where lunch was served and Dr. Sloan held an operative clinic. Six thyroidectomies were done.

The following officers were elected for the ensuing year:

*President*.....E. P. Sloan, Bloomington, Ill.  
*Vice-President*.....George W. Newell, Burlington, Wis.  
*Secretary*.....J. D. Moschelle, Indianapolis, Ind.  
*Treasurer*.....J. R. Young, Terre Haute, Ind.

#### Councillors

Dr. Wayne Babcock.....Philadelphia, Pa.  
 Dr. E. W. Rowe.....Lincoln, Neb.  
 Dr. E. R. Arn.....Dayton, Ohio  
 Dr. R. H. Stevens.....Sioux Falls, S. D.

Dr. R. A. McGillicuddy.....	Turner's Falls, Mass.
Dr. F. S. Wetherell.....	Syracuse, N. Y.
Dr. F. B. Dorsey, Jr.....	Keokuk, Iowa
Dr. G. S. Fahrni.....	Winnipeg, Canada
Dr. L. W. Frank.....	Louisville, Ky.
Dr. A. C. Scott, Jr.....	Temple, Texas
Dr. N. W. Gillette.....	Toledo, Ohio
Dr. Joy.....	Calumet, Mich.
Dr. B. T. King.....	Seattle, Wash.

A one-day meeting with a banquet in the evening will be held in Chicago, Tuesday, June 10, at the Hotel Sherman.

### PRELIMINARY CLINIC

December 17, 1923. Demonstration of Ethylene Gas given for the American Association for the Study of Goiter, at the Sloan Clinic, Bloomington, Illinois.

#### CASE ONE.

Female: Goiter non toxic. Preliminary hypodermic. Morphine  $\frac{1}{4}$ . Atropin 1/150. Patient took anaesthetic without resistance and was completely anaesthetized in  $1\frac{1}{2}$  minutes. Good relaxation, no change in color, pulse, blood pressure or respiration during the entire operation. Complete consciousness returned within two minutes after the anaesthetic was discontinued.

#### CASE TWO.

Female: Goiter severely toxic. No preliminary hypodermic. Complete anaesthesia in three minutes. No cyanosis, no change in pulse, respiration or blood pressure during the operation. Regained complete consciousness within two minutes after the anaesthetic was discontinued. Complained of considerable burning from operation wound.

#### CASE THREE.

Female: Carcinoma of the pylorus. Preliminary hypodermic. Morphine  $\frac{1}{4}$ . Atropin 1/150. Complete anaesthesia in two minutes. Complete relaxation. No cyanosis or change in respiration, blood pressure, or pulse rate during the entire operation. Returned to complete consciousness in three minutes. No post-operative vomiting.

#### CASE FOUR.

Strong muscular man 28 years of age, doing hard manual labor. Sub-acute perforation of a duodenal ulcer. No preliminary hypodermic. Complete anaesthesia in four minutes. Perfect relaxation. Cholecystectomy and gastro-enterostomy were performed. Incision closed by shoe string suture in each layer of fascia. In drawing the shoe string suture the abdominal wall raised high above the intestines. This could not occur unless complete relaxation was present.

No change in pulse, respiration, color or blood pressure during the entire administration of Ethylene. Patient returned to complete consciousness in three minutes after anaesthetic was discontinued. No post-operative vomiting.

(Blood pressures were taken on these patients that afternoon and again that evening with practically no change in findings. None vomited after operation.)

#### CASE FIVE.

Large goiter with pressure symptoms. No preliminary hypodermic. Complete anaesthesia in three minutes. No change in pulse rate, respiration or color during the administration. Returned to complete consciousness within three minutes after anaesthetic was discontinued. No post-operative vomiting.

#### CASE SIX.

Colloid goiter, non-toxic. Preliminary hypodermic, Hyoscin 1/200, Morphin  $\frac{1}{4}$ . Anaesthetised in two minutes with Ethylene. Complete relaxation. No change in pulse rate, respiration, or color of blood. After ten minutes Ethylene was discontinued and Nitrous-Oxide started on the same machine. It required more than double the volume of Nitrous-Oxide than it had required of Ethylene to keep the patient anaesthetised. Blood was darker but no cyanosis. No change in pulse, or respiration during the entire operation. No post-operative vomiting.

#### CONCLUSIONS

The advantages of Ethylene over Nitrous Oxide are:

It is a more effective and powerful anaesthetic.

It can be used without a preliminary hypodermic to much better advantage.

Its odor is not offensive after the first inhalation or two.

It is quicker in action.

It is cheaper because less is required to keep the patient anaesthetised.

Its known disadvantages are:

Its inflammability.

Its slight odor.

It was decided to feature Ethylene Anaesthetic at the annual meeting in January.

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#### OPERATIVE CLINIC NOTES

First session convened at St. Joseph's Hospital, Bloomington, Illinois, 7:45 a. m., January 23, 1924.

The meeting was turned over to the Program Committee.

It announced that the first operative clinic would begin in the large operative room at 8:00 a. m.

### OPERATIVE CLINIC

DR. E. P. SLOAN:

The first patient is a doctor's daughter, aged 19 years. She has been in poor health for about five years. Until two years ago she complained of little except nervousness. Since that time she has had marked cardiac disturbances with tachycardia on slight exertion. She is hyper-sensitive to heat and says that she "Has restlessness without reason for it." Her basal metabolism rate is plus 30. Her pulse rate 96 to 130. Her systolic blood pressure is 135.

On examination we find small thyroid with one well marked palpable nodule in the right lobe. We believe that her nervousness, restlessness and the changes in the vessel of the retina are all due to endocarditis and a similar condition affecting the blood vessels of her entire circulatory system.

In this case we will make a small incision  $1\frac{1}{2}$  inches long. Then we raise the flap, and separate the muscles by blunt dissection. Direct inspection shows that the gland has been rotated on the trachea to the right. That the trachea itself is rotated to the right. This adenoma about as large as the end of your thumb that was apparently in the lower portion of the right lobe is the isthmus. We will now separate its superior border from the trachea.

I wish you now to observe how the gland is mobilized. Since the trachea is released from the superior border of the isthmus it has rotated to the left back to its normal position. By dislocating the right lobe and bringing it forward we see that the right lobe has a normal appearance except its anterior third. The anterior third is hard and has a granular feel, typical of hyperplasia. By removing this anterior third we have left about two-thirds of the right lobe which is apparently normal. There is enough hyperplastic tissue in this portion that we have removed to account for all the symptoms in this case. Having removed this with the isthmus, and tied the blood vessels, we now dislocate the left lobe and bring it forward. Here on the posterior border of the left lobe we find a small solid adenoma. This we remove and now you see that the remains of this left lobe fold together into quite a normal shaped left lobe, although quite small. It looks like this was the original offender. It has the appearance of what is usually termed a foetal adenoma. It certainly has been present from birth or from early childhood.

Our diagnosis from conditions found at operation is toxic adenoma in the posterior border of the left lobe, with a later development of hyperplasia in the right lobe and isthmus. We will close the incision with two linear silkworm gut sutures, passed back and forth from side to side, from the outer angle of the incision, drawing the ligature back and forth subcutaneous fascia are brought together.

A running suture of catgut can be used for this, but so frequently catgut knots do not absorb in this situation that the silk worm is preferable. This fascia should be held together for ten days. If it is released earlier the fascia union is not solid and the scar will spread later, sometimes even after two to four years leaving a wide scar that is quite unsightly. The skin edge can be brought together with clips, adhesive strips, equisetine, dermol suture, or horse hair. Fine equisetine can be left in place three days without danger of scar. Dermal suture four days and horse hair can be left six days. The only objection to horse hair is that it is rather hard to handle, it takes longer time to sew the skin.

DR. WM. YOUNG (Anaesthetist.)

This patient is getting Nitrous Oxide Oxygen anaesthesia. This has been the regular anaesthetic in use here for several years. This patient received, three minutes before she was brought up, a preliminary hypodermic of Morphin one-sixth and Atropin 1/200. We took eight minutes to completely anaesthetise her. We rarely keep them in the analgaesic stage. We have them entirely asleep although not thoroughly relaxed. By pushing the gas a little bit harder we could thoroughly relax her but it is not necessary for goiter work. In abdominal work, and all of the abdominal work here is done with gas anaesthesia, we have them relaxed. I want you to notice that this patient has not been blue or cyanotic at any time. She has not moved and there is no change in color, pulse, or respiration.

While they are closing up the skin we will cut off the gas and continue with the same amount of oxygen as before. The last stitch has been made we will remove the mask. She is moving and has opened her eyes within less than one minute after the mask was removed.

DR. E. P. SLOAN:

This next case, Mrs. P. S., age 19, lives here in Bloomington. She came in with intense nervousness, irritability of the heart, fine tremor and was markedly toxic. Her basal metabolism rate was plus 48, her pulse was 146, her systolic blood pressure was 126, her diastolic was only 66. She complained of choking and swallowing sensations which could not be due to the size of the gland. She had her tonsils and adenoids removed 12 years ago, at the age of seven. The uncomfortable sensation in her throat began shortly afterward. She states that at the age of twelve her goiter was plainly visible and that it hurt her to touch it. At about the same time she began to complain of palpitation, shortness of breath and nervousness. In our opinion this patient is a typical case of strumitis and inflammation of thyroid, secondary to throat infection. This chronic inflammation of the thyroid has doubtless been present for 12 years and sclerotic changes and hyperplastic degeneration have occurred. As you see, she is not exophthalmic to an appreciable degree. She has, however, a marked endocarditis and from the history we feel certain that this

endocarditis has been present for ten years. Therefore, we assume myocardial changes have occurred. As she is only 19 we are quite confident that removal of the degenerated portion of the gland will be of marked benefit. Our definition of goiter is: *Goiter is the diseased portion of the thyroid gland.*

We will now remove the gland by technique similar to that of the previous case. You will notice upon exposure of the gland that there is a very long pyramidal lobe that extends up above the cricoid cartilage, which we will release from the trachea, as the first step in our operation. Patients with this long pyramidal tract are apparently much more likely to develop secondary Strumitis from throat infection than those without it. In fact, I do not remember of ever having seen a case of strumitis secondary to a throat infection when the isthmus was small and no pyramidal projection present.

Having mobilized the gland, we now examine both sides. I am sure that you can see from where you are sitting that the Anterior or inner portion of both lateral lobes look granular. You can see along the outer side of each lobe the line of demarcation between the diseased portion of the gland and that which is yet comparatively normal. We have now resected both lobes and have left the Posterior third portion of each lobe. The portion remaining is normal to touch and its blood supply has not been interfered with. We will close the same as the previous case.

DR. DENNIS RUPP, Anaesthetist:

This patient had one-eighth grain of Morphin, hypodermically, 30 minutes before the anaesthesia was started. The incision was made  $3\frac{1}{2}$  minutes after the anaesthesia began. You have seen that there has been no change in respiration or color. There has been no change in pulse rate or blood pressure. She is moving and has opened her eyes in less than one minute from the time the Ethylene was stopped.

It is just two minutes now since we stopped the Ethylene, and you will observe that she is practically normal, so far as consciousness and mental equilibrium is concerned. This is one of the most gratifying features of Ethylene. The patients not only come out much quicker than from under Nitrous Oxide, but they come entirely out, and are entirely conscious. She is not perspiring.

DR. E. P. SLOAN:

This third case, Mrs. J. H., Peoria, Illinois, age 24, states that a tumor was noticeable in the right lobe since 10 years of age. It became hard, somewhat painful, with discomfort upon swallowing six months ago, following a mild throat infection. Intense nervousness with marked tremor, palpitation of the heart and shortness of breath soon developed. During the last three months she has complained of choking spells when lying down. These choking spells are asthmatic in character, accompanied by palpitation of the heart and great restlessness. The gland is not very prominent but is quite hard and has



the peculiar feel on palpation that is characteristic of acute strumitis. Our diagnosis is acute strumitis following a throat infection. We do not think that the old tumor, which is doubtless a foetal adenoma, has anything to do with the toxic condition that is present. She has, of course, a marked endocarditis which is responsible for the tachycardia, and shortness of breath. Her basal metabolism rate was plus 68 when she came in and after five days preparation it was down to 44, with a pulse rate of 97.

We expose the gland in the same manner as the previous operations. You can now see the prominent pyramidal lobe, which extends up above the cricoid cartilage. This is another case of strumitis with a prominent pyramidal lobe. Apparently throat infections are prone to extend down into the thyroid when this lobe is present. This is merely an observation and I merely call your attention to it. We now separate this pyramidal lobe from the trachea as the first step in the procedure. By extending the dissection of the anterior capsule out toward the upper poles, we release the upper poles from the perilaryngeal structures.

The gland is now mobilized so that we move it up and down on the trachea over a distance of more than one inch before we encounter any resistance. We will now rotate the right lobe to the inner side and ligate the upper pole with No. 1 plain catgut. We will drop the lobe back and start in at the lower pole and flex the lobe upon itself, rotate inward, sever the lower pole and as the gland is released we get flexion, rotation and extension out through our incision and this brings all of its attachments successively into view, so that they are easily clamped and cut, and by cutting the upper poles near the ligature previously applied this lobe is delivered entirely without any tension, or rotation of the trachea. We now resect the anterior half of the left lobe in practically the same manner.

If the tumor were very large it would be very difficult through a small incision and without cutting the muscles to get to the superior pole, so we would wait to ligate the superior thyroid vessels until after the superior attachments of the isthmus and the pyramidal lobe, the attachments of the inner side of the superior pole to the perilaryngeal structures and of the thyroid to the trachea which are at about the junction of the isthmus to the lateral lobe, are severed, the lobe flexed, rotated, and the inferior pole and the attachments between the lower border of the isthmus and the trachea severed, the lobe delivered and its attachments severed in rotation from the inferior pole to the superior pole, leaving a pedicle at the superior pole containing merely the branches of the superior thyroid. Then we would ligate this pedicle and release the lobe. In other conditions by remembering and observing the same mechanical principles that the Obstetrician has in mind in a vertex presentation, it is easy to deliver any size tumor through a small opening without cutting any muscle fibers and without disturbing the respiration by traction, twisting, or pressure

upon the trachea. In our early experience we sometimes had a collapse of the trachea with great embarrassment of the respiration. In several cases so severe that we had to pass an open-ended catheter down through the trachea beyond the point of obstruction to save the patient's life, even though we had cut the muscles transversely clear out to the edge of the sterno cleido-mastoid. Since we have observed the mechanical principles that are commonly observed in obstetrics, we have not had a single collapse of the trachea and have not yet cut the muscles in over 3000 operations. Observance of the mechanical principles have made the operation an easy one in all cases when without observance of these principles it is sometimes a very difficult one.

DR. WILLIAM YOUNG, Anaesthetist:

This patient had a preliminary hypodermic of  $\frac{1}{4}$  grain of Morphin and  $\frac{1}{200}$  grain of Hyoscin forty minutes before the anaesthetic was begun. She was very sleepy from the effect of the hypodermic and her respiration was apparently affected, therefore, she was anaesthetised very quickly. The incision was made in three minutes after the anaesthetic was begun. She was given  $\frac{1}{40}$  of a grain of strychnia ten minutes after the anaesthetic was begun. Strychnia is apparently a stimulant to the respiration and seems to have a very prompt and dependable effect when the respiration is affected by Hyoscin. Within ten minutes after she received the strychnia her respiration became deeper. She required less oxygen to keep her pink and her condition has been perfectly satisfactory ever since. It requires a very small amount of gas to keep her anaesthetised.

It is just three minutes since the mask was removed from her face. She is conscious and speaking. She has made all of the vowel sounds with good, clear voice tone.

DR. E. P. SLOAN:

This fourth case, Mrs. G. H. Lincoln, Illinois, age 20. She states that she has had a goiter for 7 years, but it never gave her any trouble until about two years ago. She had recurrent attacks of tonsillitis, and developed rheumatism. Her tonsils were removed two years ago and about that time she became very nervous. Typical tremors, palpitation of the heart, shortness of breath, tenderness and sense of discomfort of her thyroid. Her pulse rate has been about 120 for the last two years. She is restless without a cause. She does not sleep well the latter part of the night, and she gives out easily. Tuberculosis has been suspected, but her temperature curve has not been consistent with her pulse rate. Exercise or excitement will increase her pulse rate but does not increase her temperature. This is a typical case of recurrent strumitis, secondary to throat infections. It has been markedly aggravated during the last year by pregnancy. Her child is nine months of age and her symptoms have been severe since its birth.

The fluoroscopic and physical examinations show her heart to be markedly enlarged. She undoubtedly had some dilatation of the heart at the time her child was born. Of course she has had endocarditis ever since the strumitis developed. The question for thought is whether iodine treatment or any other form of preventive measures would have prevented this patient from developing strumitis. If her tonsils had been removed before the infection extended from them down to the thyroid the strumitis would doubtless not have developed. Of course she would have had her simple goiter, which is a well defined tumor in the right lobe of her thyroid, but the disturbance of the heart, the tremor, the restlessness, the increased size and tenderness of the gland would not have occurred. If any form of preventive treatment would have prevented the infection of this gland and the changes that have occurred from the infection, why not depend upon the same preventive treatment for the prevention of tonsillar infection. I cannot see why it is possible to prevent infection of the thyroid by internal medication when it is not possible to prevent infection of the tonsils.

It is just two minutes since the Ethylene anaesthetic was begun. You notice that relaxation is complete. You will also notice how pink the blood is. The blood is apparently a lighter pink during the administration of Ethylene than normal. With Nitrous-Oxide there is a slightly bluish tint to the blood which in our opinion is not cyanosis but is due to the color of the Nitrous-Oxide in the blood. Ethylene appears to have the effect of making the blood a lighter pink than normal from the same reason.

We find as we expected a high long pyramidal lobe. You can see from where you are sitting this hard adenoma, about the size of a walnut with the hull on, in this right lobe. It is not the cause, however, of the hard slightly nodular areas, chain like to the touch that extends through the anterior portions of both lobes and the isthmus. I am sure that from where you are sitting you can see the line of demarcation between the portions of the thyroid that have undergone change and these posterior portions which are apparently normal. We will not ligate the superior poles because we want to leave the blood supply to the portions that are left intact.

We have now removed by the same technique as the previous cases the anterior two-thirds of the lobes and the isthmus with the pyramidal lobe.

DR. DENNIS RUPP, Anaesthetist:

This patient had no preliminary hypodermic but was given  $\frac{1}{2}$  grain of Morphin hypodermically twenty minutes ago to make her comfortable immediately following the operation. Her pulse, respiration and blood pressure have not changed. She has not been cyanotic, and has been perfectly relaxed.

She repeated the vowel sounds after me one minute after the mask was removed and is now perfectly conscious. Her consciousness

has completely returned. When a patient comes out from Ethylene anaesthetic they come completely out and do not have a border line stage like they do after most anaesthetics. All of her mental faculties are apparently perfectly normal.

DR. E. P. SLOAN:

This fifth case, Mrs. A. S., Gibson City, Illinois, age 26, has had a large goiter ever since she can remember. Ten years ago it was soft and smooth, but caused her no trouble. Her symptoms have developed gradually. She has slight tremor, pulse of 100, blood pressures: systolic 112, diastolic 76, basal metabolism, minus 10. The gland at this time is large and nodular, not tender, no discomfort upon swallowing. She has a large nodular colloid. So much of the gland is not functioning that she has less thyroid secretion than normal. We are quite certain that after the diseased or abnormal portion of her gland is removed that her basal metabolism rate will return to nearer normal. Why this happens we do not know.

We will now expose the gland. You will observe that there is practically no middle lobe, a very small isthmus. We will remove it by the regular Sloan Technique. It is impossible to get to the superior thyroid vessels with this small incision without cutting the muscle fibers with the gland in place, so we will remove the right lobe in the regular manner. Flexion, rotation, and extension enables us to sever the attachments consecutively and deliver the lobe until we have only the superior vessels that are not severed. By retraction upward with a narrow retractor we are able to ligate these blood vessels above the upper pole. Severing them, releases the right lobe completely. As we have removed the right lobe completely, we will try to find some normal tissue in the left lobe that can be left. We now have the left lobe delivered out through the incision and you can plainly see the line of demarcation between the portion of gland that has undergone the colloid degeneration and this narrow layer on the posterior inner surface. This layer is apparently only about  $\frac{1}{4}$ -inch thick but extends fully  $\frac{1}{2}$  of the way around the large tumor. We have now removed the tumor mass from the left lobe and this narrow layer falls together in such a manner that we have quite a normal looking left lobe.

DR. WILLIAM YOUNG, Anaesthetist:

This patient had  $\frac{1}{2}$  grain of Morphin, 1/200 grain Hyoscin 30 minutes before the anaesthetic was begun. She has gone through the operation in fine shape with no cyanosis and no changes in pulse, respiration or blood pressure. She repeated the vowel sounds in four minutes after the anaesthetic was discontinued.

DR. E. P. SLOAN:

This sixth case, Mrs. F., Gibson City, age 27, says she has had a goiter since she was 12 years of age. She has definite tremor of the tongue, a fine rapid tremor of the fingers with palpitation of

she came in, but after a night's rest was only 104. Her systolic blood pressure 118, her diastolic 62, her basal metabolism rate is minus 14, her hemoglobin is down to 70. She has two children, 7 and 5 years of age, respectively, and states that since the birth of her last child she has gradually run down, that she cannot stand as much as she could before and that she is always tired. She is very sensitive to heat.

Fluoroscopic examinations of the heart shows it to be enlarged with the typical curve seen in auricular-fibrillation. As she does not have auricular fibrillation, this probably means that an endocarditis with poor nutrition of the heart muscles has been present for a long time.

Operation by the same technique as the previous one discloses a large colloid goiter with some areas of cystic degeneration. Removing the abnormal or degenerated portions leaves only a small thin layer on the posterior and inner portions of each lobe. This is all of the normal thyroid gland that has not undergone degeneration. If you will notice the specimen removed closely you will see that there are no normal areas of gland substance in it.

Notice here is a parathyroid just external to the capsule. It is as large as the end of my middle finger and almost an inch long. I really do not know whether we should remove this parathyroid or not. It is certainly not normal and yet it may be the only parathyroid that she has that is functioning. We will leave it and close as in the previous cases.

DR. DENNIS RUPP, Anaesthetist:

This patient had no preliminary hypodermic and was given  $\frac{1}{6}$  grain of Morphia ten minutes ago to prevent post-operative discomfort. The incision was made two minutes after the anaesthetic was started and she is perfectly conscious and repeats the vowel sounds now just three minutes after the Ethylene was discontinued.

DR. E. P. SLOAN:

This seventh case, Mrs. O. W. C., Bloomington, Illinois, age 29, has a small sclerotic thyroid. She gives a definite history of recurrent attacks of strumitis. During these attacks she is markedly toxic with severe heart symptoms. On examination we find her with a pulse rate of 148, basal metabolism rate plus 40 and with a pronounced endocarditis. The gland is small and hardly palpable. Her history is not clear as to whether her recurrent attacks of strumitis followed throat infection or tooth infection. She states that she always became better after having teeth pulled. Her tonsils are small, ragged, and show effects of previous abscess formation. We think that her remaining teeth should be pulled and that her tonsils should be removed.

Exposure of the gland confirms our diagnosis of sclerotic degenerated thyroid. This is the fourth goiter case this morning with definite history of strumitis or disturbance of the gland from infection.

I want you to notice that in all four of these cases that a large isthmus and long pyramidal lobe have been present.

We have now removed the pyramidal lobe, isthmus and the stumps of both lateral lobes, leaving but a very small amount of tissue on each lobe. This gland was not as large as a normal thyroid, but her heart and circulatory apparatus will improve promptly. The improvement in these cases is not in proportion to the amount of tissue removed. I am sure that this patient will derive as much benefit from operation as either one of the last two who had large goiters.

DR. WILLIAM YOUNG, Anaesthetist:

She has taken her Nitrous Oxide Oxygen very nicely. There has been no change in pulse rate, blood pressure, respiration or color.

DR. E. P. SLOAN:

This eighth case, Mrs. M. A., Murphysboro, Illinois, age 21. First noticed her goiter about 2½ years ago, while suffering from recurrent attacks of tonsillitis. After her tonsils were removed two years ago she thought her goiter was going to disappear. She states that it is not as large now as it was before her tonsils were removed. She had tremor of the fingers and tongue, with twitching of the eyelids developing about a year ago. At about the same time she noticed shortness of breath upon exertion, with considerable difficulty in swallowing, especially when tired. Tight feeling in the throat when lying on her back, bothered her a great deal. She says that she had to force herself to talk and swallow. That she is very nervous and that excitement will bring on the shortness of breath at any time. She has a pulse rate of 104, with characteristic heart sounds of endocarditis. The thyroid is smooth, rather soft and is located rather far back and downward in the supra-clavicular space.

Exposure discloses a rather large diffuse colloid with some nodular areas in the anterior portions of the lateral lobes, a long pyramidal lobe and a very much enlarged isthmus. You notice that the isthmus is quite tense, and yet upon separating its attachments it merely enlarges, and since the restricting effect of the capsule has been removed it is as soft as the rest of the gland. I am not clear as to just how much this condition is due to infection from the tonsils. The four cases that we have seen this morning that were clearly secondary to infections in the throat or teeth had some features in common with this one. However we have here a typical toxic colloid. I am certain that any pathologist would report this specimen to be that of a nodular colloid goiter.

We have removed the anterior two-thirds of the lateral lobes and the isthmus and the pyramidal lobe. We are sure that she will make a satisfactory recovery. If this is a genuine colloid goiter with nodular degeneration we feel certain that she will remain well. If this condition is due to strumitis or infection we will expect the remaining portions of the gland to cause trouble in a few years.

DR. DENNIS RUPP, Anaesthetist:

This patient had no preliminary hypodermic. Incision was made four minutes after the administration of Ethylene oxygen was begun. There has been no change in color, pulse rate, respiration. She was given  $\frac{1}{2}$  grain of Morphia twenty minutes ago, hypodermically. Two minutes from the time the mask was removed she was repeating the vowel sounds. Her voice is clear. She has swallowed saliva three or four times.

DR. E. P. SLOAN:

It is now 11:30 and we will adjourn to the Mennonite Hospital at 1 o'clock.

I hope that all of you gentlemen will be back here promptly at 4:00, because we have four nice operative cases for Dr. Crotti. Those of you who have not had the privilege of seeing Professor Theodore Kocher of Berne, Switzerland, "The Father of Goiter Surgery," and Professor Roux of Lausanne, the most spectacular operator that I have ever seen operate, will have the privilege of seeing Dr. Andre Crotti, use the best features of their technique. It is almost like seeing both of them operate, to see Dr. Crotti, who was assistant to each one for three years.

DR. MOSCHELLE:

I want to express my pleasure in the number who are here. Two hundred and fifteen are here, but all have not registered. I hope that all of you will join this Society and help us to bring together Surgeons, Internists, Anaesthetists, Pathologists, and Radiologists for study and exchange of views.

WEDNESDAY AFTERNOON, JANUARY 23, 1924.

MENNONITE HOSPITAL. 1:00 P. M.

DR. E. P. SLOAN:

I am glad to see so many of you here. I hope that you enjoyed our lunch and that you are rested. We have five cases for operation and in case we should not get through in time for you to get to Dr. Crotti's clinic on time, please have no hesitation in leaving, because I want all of you to see him operate.

Our first case is Miss Mable F. of Pekin. Age 27. She has a cyst of the right lobe and isthmus the size of a very large grape fruit. She has had what has been called a foetal adenoma since early childhood. One year ago it rapidly enlarged until it is causing severe pressure symptoms and is giving her considerable pain.

We make the incision and separate the muscles by the usual Sloan technique. We find a long pyramidal lobe, reaching up above the cricoid cartilage, which we separate from the surrounding structures down to the isthmus and release the short attachment of the right lobe to the trachea. By severing the isthmus at its junction to the left lobe and releasing the isthmus from the trachea, we should

be able to dislocate this tumor. We find it rather difficult, because the tumor, although released from its attachment to the trachea, is bound down by short attachments to the lower pole, and because of its rapid growth the blood vessels and other attachment at the poles have not had time to lengthen and are holding the tumor quite rigidly.

We will now cut some branches of the inferior thyroid at the lower pole, and without much trouble we succeed in dislocating the lower end of the tumor forward. Rotating it inward brings it out through the incision. You will notice that there is just room enough for the tumor to slip through the incision. Had we not separated the attachments of the tumor to the trachea we would have to do so now, and as you see there is practically no room to get to them, we would perhaps attempt to start at this outer border and then rotate it inward and get to those attachments from the outer side. By removing it in that manner the trachea would be rotated and tension placed upon the posterior attachments, while pressure would be made upon its anterior segment.

We now get to the thyroidea Ima, the posterior capsule and finally to the branches of the superior thyroid at the upper pole. Having tied the blood vessels, we inspect the left lobe. We are surprised to find an adenoma the size of a golf ball in this lobe. There are several small cysts in the anterior portion of this lobe, so we remove the anterior half, which includes all of the diseased portion.

We used Nitrous Oxide for four cases at St. Joseph's hospital this morning and Ethylene for four. We will use Ethylene for all the patients here this afternoon. You will notice the bright pinkish red color of the blood. It appears to me that while the patient is under Ethylene Anaesthesia the blood is of a lighter color than normal. Nitrous Oxide changes the blood to a bluish color, which is not cyanosis. You may have cyanosis also, but even when the patient is not cyanotic there is some bluish discoloration of the blood, due to the gas in the blood. It is really of no importance, but disturbs an operator until he gets used to it. We have been using Nitrous Oxide Oxygen anaesthesia here since 1908 with increasing satisfaction and increasing effectiveness. We have never had a death from it, and have never been able to see that any patient was harmed by it. Without a preliminary hypodermic it is not potent enough for satisfactory anaesthesia.

This patient had no preliminary hypodermic, and as you see she is perfectly relaxed under Ethylene. She was given a hypodermic of one-sixth grain of morphin when the operation was about half over, so that she will not have immediate post-operative pain and burning.

DR. E. P. SLOAN:

This second case, Mrs. O. L., Eureka, Illinois. This patient is 42 years old and has had a goiter since she was 18 years of age. From her history it was a diffuse smooth colloid for several years, markedly increasing in size during each one of her four pregnancies. After



the birth of her youngest child, 14 years ago, it became nodular. As you see, some of the nodules have broken down and formed cysts. She is not very toxic and has a well marked tremor. Her pulse rate is around 100. She has no palpitation, even upon exertion, although she says that she tires easily.

We make the exposure by the usual method, and you see it is almost impossible with the large tumor right in the way to get to the superior thyroid vessels. Therefore, we separate the superior border of the isthmus from the trachea and the inner attachments of the superior portions from the perilaryngeal structures. The gland is now mobilized to such an extent that it can be moved up and down in the neck for a space of nearly two inches without traction upon the trachea. Now we are ready to flex, and rotate and deliver the lobe. We will first flex, rotate and deliver the lower pole of the left lobe, clamp and sever the inferior pole, the inferior attachments of the isthmus to the trachea, and after the left lobe is delivered through the opening, we clamp and sever the posterior attachments entirely. We have nothing left except the branches of the superior thyroid. Ligating these permits us to sever the attachments of the superior pole and deliver this lobe through the small opening without cutting the muscle fibers. We now remove the right lobe in a similar manner, leaving, however, a small strip of gland tissue along in the posterior border that is apparently normal. We will finish the operation in the usual manner.

DR. DENNIS RUPP, Anaesthetist:

The patient anaesthetised in four minutes. Talked one minute after the mask was removed. Condition first class throughout.

DR. E. P. SLOAN:

This third case, Mrs. J. C., Eureka, Illinois, age 43, mother of three children, has had a goiter since she was ten years of age, markedly enlarged 12 years ago. It has been gradually getting larger ever since. She states that at the birth of her youngest child, 12 years ago she had palpitation of the heart, shortness of breath upon exertion and severe nervousness for three or four years. When the goiter became larger her symptoms disappeared to a great extent. She thinks that her general health is better now than it was 10 years ago. The cystic degeneration has destroyed a large portion of the gland substance, so she is probably right in her opinion.

Operation performed in a similar manner to the previous ones. The specimen removed is much larger than a quart cup and you can see the cysts scattered all through it. The larger ones are about the size of a small orange. The interesting point in this case is that the non-toxic diffuse colloid became nodular and toxic, that cystic degeneration occurred and large areas of the gland have been non-secreting since, with marked lessening of the symptoms. She has very little thyroid tissue left, but we anticipate no myxedema or hypothyroidism

in these cases. Theoretically speaking, they will occur, but practically they never do.

DR. DENNIS RUPP, Anaesthetist:

This patient has been an ideal Ethylene case. She went under in three minutes, but had very stertorous breathing. We inserted a breathing tube and her breathing has been perfectly regular and easy ever since. Two minutes after the Ethylene was discontinued she began to gag and we removed the breathing tube. Complete consciousness has returned and she has repeated the vowel sounds. There has been no change in color or pulse rate since the operation was begun.

DR. E. P. SLOAN:

This fourth case, Mrs. L. C. G., Weldon, Illinois, age 30, has a small atrophic gland. She is severely toxic, pulse rate of more than 130 all the time, basal metabolism plus 70. This attack is of only 5 weeks duration. She has a well marked endocarditis, but she has a blood pressure of 140. Ligation might help this patient some and she might get into a somewhat better condition for operation, but with the efficient circulation which she is maintaining and with a hemoglobin reading of 90, we consider a safe risk for operation. If we were to ligate, even though she became better, yet some damage would occur to her heart and circulatory system while waiting for improvement to occur.

This is a typical case of the kind of toxic goiter that ligation benefits the least. Injection of both lobes of the gland with Quinine and Urea-Hydrochloride solution would give more benefit than ligations, but the injection would have to be complete and would have to reach a very large portion of both lobes to have the desired effect.

We expose this gland in the usual manner. Because of its small size it offers little difficulty in removal. You notice that it is hard, granular, slightly nodular, and that there is the characteristic change in the blood vessels that is always present in strumitis cases. The unusually large pyramidal lobe is surrounded by a plexus of enormously distended blood vessels. Ligation in this case would only very slightly lessen the blood supply, because these enlarged blood vessels near the pyramidal lobe would still furnish bountiful blood supply. We remove almost the entire gland and yet there is no normal tissue in the specimen removed. Closure made in the usual manner.

DR. DENNIS RUPP, Anaesthetist:

In three minutes after the anaesthetic was discontinued she was conscious and talking.

DR. SLOAN:

Gentlemen: It is now 3:30 and we are through with our fourth case. We will excuse you so that you can be in time for Dr. Crotti's operations at 4 o'clock.

# REVIEW OF ANOTHER YEAR'S WORK IN THYROID DISEASE

FRANK H. LAHEY, M.D.

Professor of Clinical Surgery, Harvard Medical School

BOSTON

In a clinic where thyroid diseases may be observed in a large number of cases, and where it is studied by a group organized for this purpose, it seems worth while to present from time to time a brief summary of the work, with such deductions from it as we feel justified in drawing, based upon that work or upon our previous experience with the disease.

We have been impressed particularly in the last year with the fact that the seriousness of cases of thyroidism is being appreciated by the medical community at large, and that active measures to check the progress of the disease are being instituted earlier in an apparently much larger percentage of cases than heretofore, owing no doubt, to increased knowledge and wider interest in this subject.

We believe that fewer and fewer patients are being subjected to the so-called "rest" or medical treatment, a method with which we have but little sympathy, resulting, as it does, for these patients—most of whom can ill afford it—in a distinct loss of time and work and a very material loss in money. In a great many cases, unfortunately, the expenditure has not only been wasted, but the delay has brought the patient to operation a much poorer risk, often with a cardiac complication as a consequence of the postponement. Another sad feature of the wasted expenditure is that many of these patients come to operation only after their financial resources are exhausted. As far as the operation is concerned, this is of little importance, since facilities for the free care of such patients can always be arranged. Postoperative rest, however, with gradual resumption of activities, has been, in our experience, an essential factor in the complete recovery, and it is here that the evil effect of the economic loss is most evident. While free operative care and immediate postoperative care are always available for these patients, a period of rest without the necessity of wage-earning.

is much more difficult and in many instances practically impossible to obtain, so that the patients often return to work much earlier than would be to their best advantage.

We have seen in the past years and still continue to see quite a considerable group of toxic cases who have been or are upon thyroid extract. We have recently had one case of primary hyperthyroidism who had received in large daily doses a total of two hundred and fifty grains of thyroid extract previous to coming to our clinic. Needless to say, her symptoms had been much intensified by this medication. Fortunately in a majority of cases the patients themselves appreciate that they are made worse by this medication, and voluntarily cease taking it. We have stressed on every possible occasion the perniciousness of this method of treatment; but again we wish to emphasize the fact that the administration of thyroid extract to toxic cases is dangerous, unjustifiable, and subject to possible serious consequences.

A somewhat similar point deserves emphasis also. The work with iodides of Kimball and Marine in Akron and its further application in Switzerland, with its possible diminution in the incidence of endemic goiter in goiter regions, offers a real boon to the residents in those regions. Yet, because of the improper comprehension of the minute doses required for this effect, there appears to be a tendency to give prolonged courses of iodide treatment, particularly to the non-toxic type of thyroid. That such prolonged iodine treatment may convert non-toxic into toxic goiter has been known for some time, and during the past year particularly we have on a few occasions seen cases in which this effect has been demonstrated. We, therefore, also wish to repeat and stress the fact that the prolonged administration of iodides may convert a simple non-toxic colloid goiter into an actively toxic one.

Basal metabolism estimations have continued to be not only of the greatest assistance but have proved of such increasing value to us that we cannot conceive of our being successful in conducting a thyroid clinic without this facility—so essential is it in the proper diagnosis and management of thyroid disease. We said last year that we did not believe that thyroid intoxication existed in the absence of an increase in the *true* basal metabolic rate. Of that we are increasingly sure, and we now

certain that when the basal metabolic rate fails to reach normal after thyroidectomy, a cure has not been accomplished, and some degree of hyperthyroidism still persists. Where this situation

#### RATE OF BASAL METABOLISM

Name—Miss C. G. Age, 18 years.

Diagnosis—*Primary Hyperthyroidism.*

Date	B.M.R.	Pulse Rate	Body Wt.	Operation
7-24-21	Plus 42	120-126	112.7 lbs.	Ligation both superior poles.
7-25-21				
8- 1-21	Plus 44	108-118	103.75 lbs.	
9- 5-21	Plus 40	98-104	112 lbs.	
9-13-21	Plus 39	108-112	113 lbs.	Sub-total thyroidectomy.
9-14-21				
9-27-21	Plus 25	78- 84	106.8 lbs.	
7- 7-22	Plus 31	80- 86	113 lbs.	Removal of thyroid tissue from both lobes.
2- 8-22				
7-14-22	Normal	76- 80	111 lbs.	
1-14-23	—10	60- 68	110.5 lbs.	

Chart showing persistent hyperthyroidism after sub-total thyroidectomy, with drop to normal after further removal of thyroid tissue.

exists, we have found that further removal of thyroid tissue has in most instances resulted in a clinical cure and a drop in basal metabolic rate to normal. We believe that the failure to obtain complete clinical cures by surgery in a certain percentage of cases in the past has been due either to insufficient removal of thyroid tissue (a consequence of natural timidity in the inexperienced thyroid operator) or to inaccuracies in diagnosis resulting in operation under the mistaken diagnosis of thyroidism upon patients with neurosis of non-thyroid origin. Elsewhere we have stated that if one accepts the dictum which we have had proved to us clinically and by many hundreds of pre- and postoperative basal metabolism estimations (we do postoperative follow up basal metabolisms on all thyroid cases, where possible, every two months for six months, and at the end of a year), that a drop to normal in the basal metabolism rate postoperatively occurs coincidentally with a clinical cure, hence indicating the absence of hyperthyroidism, and no one dealing with these cases in large number properly checked by basal metabolism estimations can doubt this—if this dictum is accepted, then the absence of an increase in the basal metabolism rate preoperatively by the same logic indicates likewise the absence of a hyperthyroidism state. Having these facts in mind, and having also in mind the possible inaccuracies of diagnosis in the borderline cases, we desire to state our conviction that without *reliable* basal

metabolism estimations. dependable evidence as to pre-operative presence and postoperative absence of thyroidism cannot be obtained.

We have seen a few cases with normal metabolic rates in patients who were quite evidently in a period of remission of the disease. In such cases, with one exception, we have not operated unless there was clinical and metabolic evidence of a return of toxicity. (The one case operated was in a young man who had so many exacerbations of the disease that he was unable to retain a position long enough to obtain an occupation. Those attacks were sufficient in severity to require varying periods in bed and were clinically typical in character.) In general, it is our opinion that in the presence of a normal basal metabolism rate, it is unjustifiable to operate upon the word of someone else that thyroidism has existed in the past. It is better, we believe, to delay, unless some other indication be present, with the possibility that the remission may be prolonged into a permanent one, and to operate only upon definite evidence of a return of the disease.

It has again been our experience that basal metabolism rate alone is not a reliable guide to the extent of surgical procedure which the patient will endure. In reviewing our basal metabolism estimations upon one thousand cases, as would be expected, preliminary surgical measures were carried out upon most of the cases with excessively high basal metabolism rates, and complete surgical procedures upon most of those with low basal metabolism rates. If, however, the basal rate were permitted entirely to dictate the extent of the surgical procedure, many deaths would have occurred in those with relatively low rates if the complete operation had been done, and many patients with relatively high rates would have been subjected to an unnecessarily excessive number of divided surgical procedures.

We have seen several pre- and post-operative cases of persistently minus degrees of basal metabolism rate as low as  $-18$  which could be elevated to normal by thyroid feeding, yet which did not demonstrably show evidence of myxoedema but appeared and felt better when their basal metabolism rate was elevated to normal by thyroid feeding. It seems possible that the basal metabolism reading may show degrees of thyroid secretion deficiencies which are not frankly evident.

We have again observed this year that following ligations even though there be clinical improvement as evidenced by gain in weight and drop in pulse rate, there frequently is little or no drop in basal metabolism rate. In practically all procedures in which any part of the gland is removed, however, an immediate lowering has occurred generally in proportion to the percentage of tissue removed.

We have continued to employ multiple stage measures in the serious cases, and feel even more certain that in the very intensely intoxicated cases it is a certain life-saving measure. Secondary thyroid operations may not be executed with the ease, dryness, and satisfactory appearance with which primary ones may. Since, however, their employment diminishes the mortality of the operation, as it undoubtedly does, the technical difficulties involved in them may be overcome through gentleness, patience and experience.

Elsewhere Dr. B. E. Hamilton, cardiologist to our clinic, has reported our experience in operating upon a group of decompensated cardiac cases with thyroidism. We believe that in this group of cases we have made more real progress in the past year or two than in any other group. Mention was not made of this group last year as a sufficient number of cases had not been done to justify conclusions. We have now operated upon forty-one cases of hyperthyroidism who have come to our clinic in varying degrees of decompensation, all incapacitated and many bedridden. With proper preoperative care they have been operated upon in stages, with but one case dying, and are all now able to be about and, in many instances, do a satisfactory amount of work.

Our efforts in the surgery of hyperthyroidism, in the past few years, have been directed largely toward the lowering of the mortality rate of the operation and the elimination of non-thyroid cases. This having been accomplished, we now feel that we have made real progress in another direction: by reaching out into this thyro-cardiac group which we have hitherto considered inoperable. As Dr. Hamilton has stated, we know of no other group of cardiac cases where it is possible to offer restoration of compensation to such a degree. It is particularly striking to see the capacity for sustained effort which these cardiac cases attain when relieved of their thyroid intoxication and persistent rapid

heart rate. There is almost no similar condition in cardiac disease where one may, by a surgical operation, remove a burden from the heart (tachycardia) which is so well calculated to use up its reserve and throw it out of normal rhythm.

We have had no tetany of any type during the last year, and have had but three cases of transitory tetany in all of our cases. We have had two cases of postoperative myxoedema, one not anticipated and one anticipated, in the removal of a large intrathoracic colloid mass in a patient previously operated elsewhere, the thyroid tissue in the normal location having been removed.

We believe that adherence to the technique published by us in Surgery, Gynaecology and Obstetrics will safeguard against hemorrhage and hematomata, two very distressing postoperative complications. We have never had a case of bilateral abductor paralysis.

During the year 1922, 450 thyroid operations were done upon 346 patients with but one death, making an operative mortality of 0.22% and a patient mortality of 0.28%. Of this group 75 patients had preliminary ligations and 271 had operations directly upon the thyroid gland. Of the 346 cases, there were 150 cases of primary hyperthyroidism, 67 cases of secondary hyperthyroidism, 115 of non-toxic goiter, 3 of thyro-glossal cysts and 5 of malignant thyroid. No cases were rejected as inoperable. Eight cases died before operations could be performed.

The only case dying during the year 1922 was one of colloid goiter in which a considerable portion of the goiter lay in the superior mediastinum and in which infection and mediastinitis occurred. Another case has also died of this disease already in the beginning of this year (1923). Previous to 1922, mediastinitis had never occurred in our clinic, in spite of the fact that the superior mediastinum had been opened a great many times in the removal of substernal and intrathoracic masses.

In both of these cases, we were not able to accomplish drainage or in any way limit the course of this infection, once it had become an established process.

Much has been written and at times almost a controversy has existed as to the relative merits of X-ray and surgery. The reports of Holmes and Means with accompanying metabolism charts indicate that it is possible in certain cases to accomplish



a lowering to normal of the basal metabolism rate, and the authors state a relief of symptoms. However, we are definitely opposed to X-ray treatment of thyroidism for the following reasons.

The purpose of X-ray treatment in thyroidism is to check thyroid secretion by destruction of thyroid tissue or by inhibition of secretory activity. This destruction of tissue, when it occurs, must be accomplished gropingly, striving to arrive at that desired point where enough thyroid tissue is prevented from secreting, so that hypersecretion is avoided, yet, where sufficient tissue is left unaffected so that myxoedema shall not result. We believe that such a method is not comparable in certainty and accuracy with surgical removal, where one may be sure of the amount removed, the amount remaining, and the supremely important factor of the activity of the type of tissue being dealt with. We further believe that our own unsatisfactory experience with removal of limited amounts of thyroid tissue may be repeated in many of the cases now considered cured by X-ray treatment. It has been repeatedly demonstrated to us that relief of hyperthyroidism for a considerable period of time may often be accomplished by hemi-thyroidectomy, but that recurrence frequently occurs in the remaining lobe.

Up to 1921 we employed an operation in which from two-thirds to one-half of one lobe of the thyroid was left. In a great majority of cases this accomplished an immediate relief of symptoms. We have, however, seen a considerable number of recurrences of hyperthyroidism in this remaining lobe of thyroid tissue, a condition which has been relieved by removal of a portion of the remaining lobe. So impressed have we become with the necessity of removal of large amounts of thyroid tissue for rapid, complete, and permanent relief, that we have in the past three years changed and adjusted the technique of our operation to meet this need, so that the smallest possible amount of thyroid tissue is left that will prevent the appearance of myxoedema. This, we believe, is essential if one is to produce a complete and lasting relief. As stated above, we cannot conceive of accuracy of X-ray dosage to such an extent as to be comparable with surgery in accomplishing this purpose.

Furthermore, during operations upon thyroids we are often surprised to find many cases possessing deep intrathoracic ex-

tensions whose presence we in no way suspected previous to operation. These we believe are a serious menace to life, and are in themselves an indication for surgery. Not infrequently, also, we have believed that a given case was of the hyperplastic, primary hyperthyroidism type, only to find at operation that it was a case of multiple adenomatous goiter with secondary hyperthyroidism. Both of these types of cases may not be discoverable by X-ray and the adenomata cannot, of course, be removed by X-ray.

As to mortality, we believe that the death rate in our clinic and in many of the large organized clinics, dealing with thyroids in numbers, is so low that it does not constitute an argument against surgery. In fact, the comparison of mortality in the two methods is by no means possible yet, as when X-ray treatment fails, the uncured patient is passed on to the surgeon for operation and any attendant risks.

We believe that the uncertainty of cure, the length of time necessary to ascertain the value of X-ray treatment in a given case, and the loss of time and money constitute weighty arguments against this form of treatment. We have repeatedly stated and firmly believe that hyperthyroidism is a sufficiently serious disease, and one so capable of being rapidly converted into a state in which operation is either extremely risky or not possible, that the method of treatment to be applied to it is the one which most quickly, most certainly, and most completely, removed the intoxication which produces the ill effects. That surgery meets that need far more satisfactorily than any other measure no one who has dealt with these cases in any number can doubt.

Further, we do not believe that the arguments against X-ray treatment are by any means offset by the stated benefits of this form of treatment, such as absence of scar, escape from operation, and avoidance of hospital stay.

Finally, we are absolutely convinced that centralization, individualization, and organization are the salvation of goiter cases which are to be treated surgically.

#### CONCLUSIONS.

Thyroid extract is contraindicated in toxic cases and prolonged iodine feeding may convert non-toxic into toxic goiter.

Hyperthyroidism does not exist in the absence of increased basal metabolism rate and cures of hyperthyroidism are not

accomplished without returns of basal metabolism rate to normal, provided there are no conditions other than a thyroidism elevating it.

Basal metabolism readings are of great value in neurosis simulating thyroidism, in that the true basal metabolism rate in the neurosis is normal.

Basal metabolism readings uncorrelated are not a reliable guide to the number of operations a patient will stand.

Minus degrees of basal metabolism rate may exist in patients free from clinical evidence of myxoedema, yet made subjectively better by raising the rate to normal with thyroid feeding.

Multiple stage measures are life-saving procedures in severe hyperthyroidism.

Thyro-cardiac cases first seen in decompensation may be restored to striking cardiac capacity if it is possible by thyroidec-tomy to remove the intoxication and to restore the heart rate to within normal limits.

The most dreaded, uncertain and uncontrollable factor in our clinic today is mediastinitis.

The moderate values of X-ray treatment are more than outweighed by its disadvantages.

Thyroid surgery done in a general surgical clinic equipped for the care and study of these cases will show few failures to cure and a mortality rate rarely over and in most cases under one percent.

# AN ANALYSIS OF TYPES OF GOITER WITH INDICATIONS FOR TREATMENT

BY

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Goiter is not such an innocent disease as the public usually considers it. It is too seldom realized that goiter, especially in places where it is of endemic nature, influences not only the bodily but also the mental status of a people to an extent that no other endemic disease is known to affect them, and that goiter must therefore be considered as a national drawback.

We know too little concerning the etiology of goiter, yet we have means of curing the disease if recognized and treated early, but of this fact also the public is likewise too generally ignorant. There exist so many and partially justified fears of goiter treatment that many persons feel that it is best to leave a goiter alone. They regard it more as a physiologic condition than a disease.

It is therefore most urgent that doctors explain to a larger portion of the public that goiter *must be treated*, and treated *early*, or the progeny of those suffering from goiter will be threatened with the disease, and that such treatment need involve no danger to the patient if administered in the right manner and at the right time.

In the United States, in spite of repeated advice from physicians, nothing adequate has as yet been done in this matter. Many physicians have lately tried to emphasize the importance of such treatment in the schools. Among them may be mentioned Roux, Klinger, Weith, Fritsche, Kimball and Marine, but it is ridiculous to expect results after a few weeks of such treatment, as such rapid results could only be achieved from overdoses of iodine. Lasting results will come only by the use of small doses of iodine begun during early infancy and continued for a long period of time, perhaps even throughout life.

In this connection it is important to remember that goiter is a result of increased thyroid function. It is therefore clear

method of prevention has never come into general use in the United States.

*Administration of iodine.*—By way of introduction we must state that all successful goiter medication contains iodine. Even when the medicine contains other substances, and iodine is not mentioned, it is always present if the medicine gives any results. We wish to particularly emphasize that in practically all of these iodine preparations the dose of iodine is too large.

The following methods have been used in our out-patient department at the hospital with good results, or have been advocated by experienced goiter therapeutists:

1. Iodized salt.—Ordinary table salt containing not more than 0.5 gms. or  $7\frac{1}{2}$  gr. of sodium iodide to the pound. We advise the family to use this salt instead of ordinary table salt as a routine unless some member of the family has an adenomatous goiter, in which case that person should use an individual salt cellar, as the administration of iodine in adenomatous goiters is likely to produce hyperthyroidism, as will be explained later.

2. Giving of 2 grms. or 30 grains of iodine spring and fall.—This method has been advocated by Marine, Lenhart and Crile. They usually advise the taking of this amount in a saturated solution over a two weeks' period of time. Occasionally symptoms of iodism will develop due to the large dosage. We do not feel that this method is practicable for general use.

3. Administration of tablets containing iodine in the schools.—This certainly would seem to be an ideal method. It would be more than the sporadic use of iodine as now practiced. It consists in the giving of a tablet containing  $1/10$  grain of iodine daily, five days in the week, and seven, eight or nine months in the year, depending upon the length of the school term. This dose may seem small, but it is sufficient to carry on the iodine metabolism of the thyroid gland. The tablets should be administered by the teacher at a definite time each day.

4. Inhalation of iodine.—This is a method in general use in Switzerland. Small vessels with perforated tops, containing salts of calcium, potassium and sodium iodide are exposed to the air, thus giving off the fumes into the air. If goiter is to be permanently avoided this inhalation of small amounts of iodine must be repeated and continued over long periods of time, or even throughout life.

5. The administration of thyroid gland preparation.—It has been found that dried thyroid substance from animals has a goiter-diminishing effect, and its significance in goiter pathology has been emphasized.

Can thyroid gland preparation be of use in prevention of goiter? That this is possible is no longer open to question, but this method has greater difficulties than those encountered in iodine administration, as in large doses it is even more injurious than iodine. As we are dealing with an organic substance, and as the animal glands from which the extract is made vary widely in their chemical composition, accurate dosage is difficult. Of course, none but an assayed preparation should ever be used.

The use of thyroid extract in the prevention of goiter has, however, an important place. It is indicated when signs of diminished thyroid function have been observed in the goiter of a goitrous family; that is, in families where goiter has existed for generations. In such cases it is strongly urged to treat the pregnant women with thyroid extract so that the children may not be born with goiter, a goiter tendency, or what is still worse, with a thyroid deficiency.

In such children iodine prophylaxis for goiter does not suffice, and they must be treated with thyroid extract from early infancy, if the thyroid function is to be kept normal and the child is to develop normally, mentally and physically.

Such treatment should only be administered under constant supervision of a physician, and never by druggists or parents without medical advice.

B. The treatment of already existing goiter.

1. *Treatment of goiter with iodine.*

It is, of course, much easier to prevent a goiter from developing than it is to cure one already formed, especially as goiters lead to degeneration. It has been shown by several workers that the thyroid gland shows an increase of degenerated tissue with each successive exacerbation. Iodine has less effect on degenerate tissue than on normal tissue, so that in order to be successful, goiter treatment must be instituted early. One other consideration must be taken into account if the goiter is to be cured, i. e., to disappear, and that is that iodine must be taken in continuous *small doses*. Practically this is not so easy, however, because people lack the necessary patience. If they see no imme-

diate result they discontinue the treatment, and too often resort to some of the numerous quack treatments for goiter. The result of such treatments is a rapid disappearance of the goiter, but, alas, also a just as rapid recurrence with a progressively diminishing effect of the intensive iodine treatment for every recurrence. It has been proved by the author, by Baumgarten, des Ligneris, Marine and Lenhart, that such large doses of iodine injure the normal thyroid tissue even more than they affect the abnormal tissue, and cause degeneration.

As we have mentioned before, iodine loses its efficacy when the tissue is degenerate, but this is not the worst result of treatment of goiter with large doses of iodine. Much more serious are the effects produced on the general condition of the patient. Iodism and hyperthyroidism have already been mentioned in this connection when too large doses of iodine were used in the effort to prevent goiter. Even worse effects are produced when a goiter already exists. Only too often the patient loses in strength and health as rapidly as the goiter disappears; he loses weight, becomes violently excitable, with a rapid pulse and high tension heart beats, with sweating diarrhea, sleeplessness and great weariness. In other words, he has developed what Theodor Kocher calls "Iodine Basedow's Disease," which lasts for months, and may leave permanent heart trouble.

Probably the administration of iodized salt is the treatment of choice, as it can be safely continued throughout life. When after several years it becomes unnecessary for the parent, the treatment should still be kept up for the children as a prophylactic measure.

One of the methods of giving iodine,—that is the iodine ointment which is applied by rubbing on the skin over the thyroid, is only mentioned to *condemn it*. In the first place, massage of an active goiter is bad treatment. Secondly, you cannot estimate the amount of iodine which the patient is getting.

### 3. *The Treatment of goiter with animal thyroid extract.*

P. Bruns demonstrated for the first time in 1895 that the administration of dried thyroid substance could cause disappearance of goiter. Five years previously Murray discovered that in individuals lacking the thyroid gland, by regular administration of animal thyroid substance the serious symptoms resulting from such a lack should be materially benefited.

The reducing effect of thyroid substance in goiter depends on a similar action as it acts as a substitute for the thyroid whose function has been disturbed by the goiter, and thus decreases the tendency to goiter development.

There is still another indication for treatment of goiter with thyroid extract. When degeneration of the goitrous tissue takes place, which may occur as a result of overdoses of iodine, the organism, in spite of the enlargement of this organ, is no longer able to produce enough thyroxin. The results of this impaired thyroid function now begin to tell on the general condition. The symptoms are numerous. They show themselves principally as bodily and mental fatigue, in faulty circulation, neuralgia and rheumatic pains. Many goiter patients suffer from these symptoms, and may be benefited by treatment with thyroid extract. Usually they are treated with all kinds of remedies with no result, as they themselves as well as the physician too often ascribe these symptoms to other causes. It cannot be too often repeated that such thyroid therapy must not be attempted without the direction of a well-informed physician.

The adenomatous or nodular goiter is the most common type of goiter needing surgical treatment. It can be conveniently divided into two sub-classes for study—simple adenoma and adenoma with hyperthyroidism. This type usually develops about the age of puberty. It may grow slowly or rapidly, and frequently produces the pendulous goiter so often seen, while a small adenoma occurring in the isthmus of the thyroid may cause serious embarrassment to the breathing. The adenomata are usually multiple, and clinically are recognized by multiple hard, irregular and movable nodules occurring within the thyroid gland, although some of them may be soft and cystic. In contrast to the symmetrical colloid type they are usually asymmetrical enlargements. They may remain quiescent for years and produce no symptoms, or they may become rapidly toxic following any of the acute infections such as tonsillitis, influenza, pneumonia, etc. They are frequently "lighted up," so to speak, by the injudicious use of iodine, either internally or externally. Their treatment is definitely surgical, but operative interference should be avoided, especially before the age of twenty-five, since during the developing period of life the thyroid is most essential. But should pressure, deformity or toxicity develop, a



double resection should be performed, conserving as large an amount of thyroid as possible, since some adenomatous tissue must be left, while in older individuals all adenomatous nodules would be removed. Recurrence is, of course, more likely when operated early before a more complete removal can be performed.

Adenoma with hyperthyroidism usually occurs in individuals who have had the adenoma in the thyroid gland for several years, without symptoms. They usually become toxic following one of the acute infections and are frequently not recognized. They may be recognized clinically by marked cardiovascular changes, rapid loss in weight, gastro-intestinal symptoms, increased metabolism and increased nervous excitability. The presence of the above symptoms without a palpable thyroid enlargement in the neck should suggest the possibility of an intra-thoracic goiter or other accessory goiters. Following partial thyroidectomy, the metabolic rate rapidly returns to normal, and the gain in weight is quite rapid. Of course, if the cardiovascular disturbance is well marked and anatomic changes have occurred, the restoration to normal will not be complete. The results of *early* operation in adenoma with hyperthyroidism are 100% if we rule out the accidents of surgery, namely, hemorrhage, infection and embolus.

The results are not so good if the toxicity has been excited by repeated courses of iodine therapy. Strange as it may seem, we still see many cases of adenoma, with or without hyperthyroidism being treated by iodine. This form of treatment of this group of cases, especially in individuals past thirty-five years of age, cannot be too strongly condemned.

Exophthalmic goiter or Graves disease is characterized by a definite train of signs and symptoms, the most prominent of which are tachycardia, exophthalmos, muscular tremor, weakness, vasomotor, excitability, disorders of metabolism, and many manifestations of disturbances of the nervous system which are associated with hyperplasia of the thyroid gland, and in many cases by disturbances in other glands of the endocrine system. A small group shows definite hyperplasia of the thymus gland which should be excluded before surgical intervention is advised. An X-ray examination to exclude this complication should be a routine procedure. On one of our own cases, with only slight improvement after thyroidectomy, further X-ray examination

disclosed a large thymus, and following X-ray therapy there was prompt and satisfactory recovery.

The exact etiology of Graves disease is unknown, but infections, nervous shock and thyroid toxins seem to be the chief causes.

Clinically, there seem to be two types of this disease; the one, characterized by its chronicity, is gradual in onset and runs an even, usually mild course, and rarely develops a thyroid crisis; the other, sometimes called the remittent type, is characterized by one or more fulminating attacks induced by shock, fright, sickness, overwork, acute infections, and so forth.

The symptoms of the latter group gradually increase in severity, with or without the appearance of goiter or exophthalmos, until a crisis occurs, which is characterized by the sudden exacerbation of the symptoms, with the addition of nausea, vomiting, diarrhea and extreme debility. If the patient survives the crisis, a period of partial remission of the symptoms follows which may persist for months, but is usually followed by recurrence of varying intensity. The remission may, however, be complete, with the patient symptomatically cured, the disease being quiescent, or the remission may be only partial, with chronic invalidism.

Medical treatment of Graves disease is still advised by some internists. It consists of rest in bed, ice cap to the heart and the thyroid gland, low protein diet, and administration of lugols solution gtts. 10 daily. If, after a conservative trial of four to six weeks, the patient has not markedly improved as evidenced by gain in weight, slowing of pulse and recovery of nervous equilibrium, it should be discontinued and surgery advised.

X-ray treatment has been tried by several clinicians of repute, but the larger goiter clinics have discontinued its use. It should never be used except in the hyperplastic cases—Graves disease. Definite dosage is problematical and the destruction of the thyroid tissue cannot be estimated or controlled. We have seen one case of tetany result from X-ray treatment. Our results have been disappointing, and do not compare favorably with surgery.

The treatment is surgical, but all cases cannot be subjected to operation by any set rule; each case must be individualized, and herein lies the whole solution of this difficult class of cases.

A certain percentage of cases will seem to recover without treatment, while others run an acute course, and terminate fatally in spite of all treatment.

An analysis of statistics from various clinics would seem to indicate that seventy percent are cured by surgery, twenty percent are improved, and ten percent are not benefited or have recurrences.

**IODIN IN PUBLIC WATER SUPPLY.**—Rochester, N. Y., is attempting to solve its goiter problem by putting iodine in the public water supply. Water from Hemlock Lake, which flows into Rush reservoir about ten miles south of Rochester, has a normal iodine content of about 1 to 2 parts per billion. This is increased to about 50 parts per billion by the addition of sodium iodide. The amount of water entering the reservoir is determined at the Gate House by means of a "thin edged weir" or dam. The city was using when iodine was added about 25 million gallons of water a day, to which 16.6 pounds of sodium iodide was added daily for three weeks. The salt was simply placed in a cotton bag and held in the water above the dam until dissolved, which required about three or four minutes. The cost is estimated at about 1 cent per person per year, using the iodine salt six weeks in the year. A resurvey will be made next year to determine the results obtained. Copied from *A. M. A. Journal*, Nov. 17, 1923.

# DIFFERENTIAL DIAGNOSIS OF INCIPIENT TUBERCULOSIS AND INCIPIENT GOITER

BY

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Ten days ago I had an opportunity of making the rounds in the Mayo Clinic, Service of Dr. Plummer, and saw there probably one hundred cases of goiter. I mentioned to Dr. Walter Boothby, who is associated with Dr. Plummer, that I was on the program to speak before this Society on "The Differential Diagnosis of Incipient Goiter and Incipient Tuberculosis." He was rather surprised that there should be any difficulty in differentiating the two conditions; that there are certain symptoms that clearly differentiate the early goiter and certain other symptoms that clearly distinguished the early case of tuberculosis. However true this may be, mistakes are very frequently made.

I happen to be the Director of the Ottawa Tuberculosis Sanatorium, an institution for the treatment of pulmonary tuberculosis. In this sanatorium we have forty-five patients at the present time, and three of these patients have scars on their necks of previous goiter operations. All three of these cases have at this time definite physical signs of pulmonary tuberculosis. Is it possible that in these three instances an early tuberculosis was mistaken for early goiter, or is it possible that they had both tuberculosis and goiter? That, of course, I do not know. However, if they had pulmonary tuberculosis at the time of the operation it can be stated without question of contradiction that the shock of the operation was certainly not beneficial, and probably harmful to the patient's resistance to tuberculosis. On the other hand, how frequently is early goiter mistaken for pulmonary tuberculosis?

In 1921, Dr. Gay (Reports U. S. P. H. S.), went over the records of 1700 cases in which a diagnosis of pulmonary tuberculosis had been made, and in these 1700 cases he found 176 mistakes, or 10.4 per cent. In this group of 176 cases he found that 32 had chronic bronchitis; 18 had cardiac disturbances; 15

had upper respiratory tract infections; 15 had neurasthenia; 12 were suffering from interstitial pneumonia; 10 were cases of bronchiectasis; 11 were non-tuberculous infections of the lungs; there were four cases of asthma; four cases of lung abscesses; and three cases of gastric ulcer, and of this total number of 176 cases, four were ultimately diagnosed as hyperthyroidism, or in the latter instance an error of 4/10 per cent. This is indeed a small error, but one that must be taken into account, and the possibility of mistaking an early tuberculosis for an early goiter must always be kept in mind.

From my own experience, however, in seeing cases admitted to a sanatorium for the treatment of pulmonary tuberculosis, and from the statistics above quoted, I think it reasonable to assume that there is a higher percentage of error being made by goiter specialists and general surgeons in mistaking early tuberculosis for early goiter than there is on the part of internists and specialists in tuberculosis in calling early goiter an early tuberculosis. Can the two diseases be readily differentiated? In many cases, it is true that they can be, where active symptoms of the disease are present; such, for instance, as well-marked physical signs in the chest, typical temperature curve, definite X-ray findings in the lungs, tubercle bacilli in the sputum, etc., should not, under any circumstances, be confused with goiter. It is also true that in cases of well-marked hyperthyroidism that a diagnosis can be made across the room, but this is not true in the early case.

What are the symptoms of early tuberculosis? Lassitude, fatigue, loss of appetite, fever, loss of weight, and weakness. These can also be the symptoms of early goiter. In addition, however, there are other symptoms in goiter that we do not have in tuberculosis ordinarily, such as tremor, palpitation, and increased appetite.

It may be interesting to list in parallel columns the prominent symptoms in the incipient stage of both diseases.

#### SYMPTOMS OF

Tuberculosis	Goiter
Fatigue, lassitude, lack of appetite.	Fatigue, lassitude, increased appetite.
Weakness, nervousness, fever.	Weakness, nervousness, no fever.
Rapid pulse, loss of weight, cough, night sweats, dyspnoea.	Rapid pulse, loss of weight, cough, sweating, dyspnoea.
	Palpitation, tremor.

On the basis of these two groups of symptoms there are certain things, particularly palpitation, tremor, heart changes, and increased appetite that are almost always present in toxic goiter that readily differentiate the early goiter from the incipient tuberculosis, if a careful history is taken.

When the basal metabolic rate was introduced I was immediately impressed with its possible value as a method of differentiating tuberculosis from goiter. In my experience with it, however, during the past two years, the results have been unsatisfactory. I have made determinations of the basal metabolic rate in forty-five cases of early pulmonary tuberculosis. Three successive determinations were made in each case on three successive days. All of the determinations were made by the same technician under exactly the same conditions. In a majority of these cases it was found that the metabolic rate was ten per cent below normal. In several instances, however, the rate was plus ten per cent. In several instances, however, the rate was plus ten per cent to plus forty-five per cent. In these cases the determinations were repeated with exactly the same results as before. There were no signs of goiter. From these determinations I was forced to conclude that either our method and technician were unreliable, or that we were dealing with cases in which tuberculosis and goiter were both present. I am inclined to believe that our aberrant results were due to poor technique rather than the presence of the two diseases, as there were no confirmatory signs of goiter present in any of these cases. Perhaps if we had used a better apparatus, such as the Haldane-Tissot, rather than the Handy Benedict, our results would have been more reliable, but who is there in a tuberculosis sanitarium that has the time to carry out elaborate gas analysis determinations?

Until an accurate, simple method of determination of the basal metabolic rate can be perfected, it will be impossible for the ordinary practitioner to utilize this method as a general diagnostic test.

I am of the opinion, however, that a careful study of the symptoms in any case will make it possible for us to make an accurate, differential diagnosis between incipient goiter and in-

ipient tuberculosis, and by more careful study, perhaps, we will be able to keep some cases of incipient goiter out of the sanitarium for the treatment of tuberculosis, and we may likewise be able to save a number of cases of early pulmonary tuberculosis from operations for goiter. We must, however, keep in mind that it is possible for an early case of tuberculosis to also be suffering from goiter, or a case of goiter may also be afflicted with pulmonary tuberculosis.

# THE ROENTGEN TREATMENT OF TOXIC GOITER

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LINCOLN, NEB.

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## INTRODUCTION

No discussion on the treatment of goiter should fail to pay tribute to the names of those pioneers whose names stand like milestones in the historical survey of goiter. In 1786 Parry recognized exophthalmic goiter. Graves in England in 1835, and Basedow in Germany in 1843, studied it more carefully. Moebius in 1886 brought forth the theory that the morbid function of the thyroid caused an intoxication. He called it hyperthyroidization, which is the syndrome today spoken of as hyperthyroidism or thyroid intoxication.

Recent literature is fresh with the reports of thyroid research. Let me call attention to the large number of articles in current literature on the roentgen treatment of thyroid intoxication. Within the last ten years the advancement in knowledge of the chemistry, the histopathology, the physiology and the classification of thyroid disease has no parallel in medical science.

Kendall in 1914 separated a pure chemical compound thyroxin from the thyroid gland. Subsequently he proved that thyroxin is the active principle of the thyroid gland, and demonstrated the chemical composition of this compound. Plummer by his sagacious reasoning has correlated the recent findings of science and has developed a new philosophy of the disease, which in the main has been acceptable. With the added interest in metabolic studies of the alterations in metabolic



rates by certain thyroid states, the work of Boothby and Sandiford at Rochester, DuBois at Cornell, Harris and Benedict at Carnegie Institute, Deyer at Oxford, England, and others have completed work of great practical value. The researches in this country of Halsted, Cunningham, Carlson, Marine and Cannon are worthy of our greatest admiration.

#### PATHOLOGY

A relative view of all thyroid diseases is necessary to treat thyroid intoxication. Plummer's clinical classification is chosen because of its wide adoption and its comprehension.

1. Diffuse colloid goiter.
2. Adenomatous goiter with hyperthyroidism.
3. Adenomatous goiter without hyperthyroidism.
4. Exophthalmic goiter.
5. Myxedema.
6. Cretinism.
7. Childhood myxedema.
8. Thyroiditis.
9. Malignant disease of the thyroid.

Some of these names represent pathological conditions and some clinical conditions. In fact, each name represents a disease with its etiology, pathology, symptom complex, prognosis and treatment.

Certain anatomical considerations should be kept in mind. The thyroid gland is ductless. Its secretion communicates with the outside tissue only through its walls. It consists of epithelial tissue bound in a capsule-like lymphoid tissue. It is dumb-bell in shape, lying across the trachea, with the bar below the larynx, both lobes investing the trachea. It is abundantly supplied by blood vessels and nerves buried deep in the vital tissues of the neck. The normal gland consists of acini containing colloid and lined with relative inactive cuboidal columnar epithelium, supported by connective tissue similar to that of other parenchymatous organs. The gland is abundantly supplied with reserve tissue. Three-fourths of it has been removed without any demonstrable disturbance in the physiology of the body or any change in the glandular tissue of the remaining thyroid. The thyroid undergoes periods of activity and repose, stores iodine and colloid. In periods of stress it uses stored iodine and delivers thyroxine to the blood stream. The

mechanism of stimulation is not known. To one accustomed to viewing secreting microscopic sections of glands, it has the appearance of a quiet inactive gland.

In the examination of thyroid tissue there is nothing pathomonic to tell of the presence of thyroid intoxication or exophthalmic goiter, nor to indicate the clinical state or degree of intoxication. Hypertrophy and hyperplasia are found in characteristic manner in adenomatous and exophthalmic goiter, but at the same time they are sometimes present in other types and cause no thyroid intoxication.

However, the pathological findings are fairly constant and reduce themselves to simple types, with all other tissue changes but degree of modification. The primary types found are—colloidal, adenomatous, and exophthalmic. Or, colloidal, nodular, and diffuse, showing hypertrophy and hyperplasia.

In the colloid type there is an increase in the intra-alveolar colloid. In the adenomatous new cells develop usually localized but often diffuse, thought by some to be embryonic resting cells and hence liable to perverted cell activity. Diffuse parenchymatous hypertrophy, symmetrically involving the entire gland together with hyperplasia, is the characteristic type of so-called exophthalmic goiter. But three primary pathological processes are possible—hypertrophy of the alveolar epithelium, increase in intra-alveolar colloid, and development of new alveoli. Hyalinization, cystic degeneration, fibrous formation, calcification and malignancy may arise, but are incidental to the primary pathological changes that may occur in any glandular degeneration or new growth.

The physiological changes associated with these pathological changes are:

1. Hyperthyroidism, or that syndrome which is identical with the administration of thyroxin and rarely seen except where hypertrophic or adenomatous changes in the thyroid are found.

2. Hypothyroidism, or that syndrome which may be considered the opposite condition, and causing a symptom complex, varying in degree but occurring as thyroxin is depleted in the tissue.

3. Exophthalmic goiter, which may be called a hyperthyroid state plus something yet in controversy as to cause and action, but giving the well known signs.

Cunningham and Carlson in trying to produce experimental thyroidism found that the administration of thyroid extract never produced exophthalmic goiter. Cannon produced some of the signs of exophthalmic goiter by anastomosis of the phrenic and cervical sympathetic nerves. Marine's experiments reproducing the same work were unsuccessful. "The experiments were so carefully done that, at present, the various hypotheses, assuming lesions in the sympathetic nerves and especially in the cervical ganglia as accountable for the disease or for hyperplasia of the gland are without experimental foundation." (Nellis B. Foster.)

We are compelled for the present to fall back upon the theory advanced by Plummer, that the explanation of hyperthyroidism in exophthalmic goiter lies in the production not of thyroxin, but of an incomplete molecule slightly different in chemical composition.

#### THYMUS

The thymus gland is normally of little significance in the adult. Its extirpation in animals is known to have brought about no detectable change in any body function or organ. Its rôle in the thyroid disease is not known, but its presence in sixty-five per cent of the cases of exophthalmic goiter operations and its importance in roentgen treatment, make it very probable that some pathological process in it goes along with thyroid disease.

Marine in 1888 suggested the regrowth of the thymus in Graves' disease. Thymic hyperplasia is now recognized as frequent. Blackford noted it in all younger individuals afflicted with Graves' disease. He believes that a persistent thymus is one of the characteristic findings in thyroid intoxication, the average weight in twenty-four cases being thirty-six grams. Thymus hypertrophy is usually found in all cases up to forty. Beyond the fourth decade an enlarged thymus occurs in perhaps half of the cases that come to autopsy. This persistence of the thymus is not characteristic of the toxic form of goiter, since it is occasionally found with simple or colloid goiter.

Blackford summarizes that every patient under forty with thyrotoxicosis, and every patient under thirty with simple (colloid) goiter examined postmortem showed evidence of hypertrophy of the thymus. Over forty years of age one-half of

the cases of thyrotoxicosis and three-quarters of the cases of colloid goiter showed enlarged thymus at postmortem.

#### THYROXIN

The normal action of the thyroid influences growth of the skeleton, the activity of all tissues, including the central nervous system, secondary sex characteristics and mature life. It controls metabolism. Its interrelations with other glands are problems yet for study.

The disturbance in physiology and the developing syndromes of the various thyroid diseases may be understood in terms of thyroxin. The story of thyroid intoxication is locked up in the knowledge of the composition, elaboration, storage, liberation and action in the body tissues of the chemical compound thyroxin. This important compound is manufactured in the thyroid gland and may be found in the body tissues in very minute quantities. The thyroid has no other known function than to produce thyroxin. It is stored in the colloid of the gland. The function of thyroxin seems to be to activate the function of the body cells or to furnish actual energy. When in excess hyperthyroidism is the result, and the basal metabolism rate is above normal. When it is low or absent, the metabolic rate is low.

#### METABOLISM

Disorders of the thyroid gland are differentiated today by alterations in the basal metabolism rate. An increase or a decrease in the thyroxin output is accurately gauged by this method, giving the true status of severity. The basal metabolism rate is the mathematical expression representing the basal heat production of an individual under standard conditions. It is like the thermometer, measuring the heat phenomena inherent in the living organism. Workers in clinical calorimetry differentiate three classes of metabolic rate—normal, increased, or diminished. For practical purposes, plus 10 to minus 10 may be considered normal or a possible variation due to the method or the difference in technique. Minus 10 to minus 40 are low ranges or pathological thyroid. Plus 10 to plus 125 are the possible high ranges.

In health, variations are slight. The basal rate is more constant than the pulse or temperature. The slightest change in the chemistry of the blood causes the most grave disturbance.

The changes in the iodine content of the thyroid are comparable in delicacy.

Of the diseases so far investigated, the following are characterized by an increased metabolic rate: Exophthalmic goiter, hyperthyroidism of adenoma, the actual stage of acromegaly, and all febrile conditions. In other diseases, such as essential hypertension, pernicious anemia, leukemia, diabetes, and possibly a few others not yet investigated, a basal metabolic rate lightly above normal may occasionally though consistently be met with. After more than 20,000 tests for basal metabolism by Boothby, and his co-workers, it was found that 95 per cent of all abnormally increased basal metabolism rates are due to hyperthyroidism, either exophthalmic in type or from thyroid adenoma, if a febrile condition is eliminated by the thermometer. Then for practical purposes an increased basal metabolic rate means exophthalmic goiter or adenoma of the thyroid, or some mixed type, providing the factors enumerated have been eliminated. Of particular value is the metabolic rate in the elimination of those cases called circulatory asthenia, effort syndrome, disordered action of the heart, cardiac neurosis or nervous instability or neurasthenia. In these conditions the basal metabolism is not disturbed.

The metabolism test may be called the quantitative estimation of the thyroid function. It is the gauge for treatment. It helps the clinician to visualize the progress a patient is making. It clinches the diagnosis in doubtful cases.

For one treating a large number of thyroid cases, the use of the metabolimeter is a necessity. Like the microscope and the electrocardiograph, it is necessary for the one who needs it. Even long experience with the clinical signs of hyperthyroidism does not develop accuracy in estimation of the metabolic rate. Experience gives qualitative skill, but not quantitative ability.

#### MEDICAL TREATMENT

The object of treatment in thyroid intoxication is threefold—to reduce the output of thyroxin from the gland, to permanently lessen the function, and to conserve the other organs of the body.

Essential in every case is the task of cleaning up all focal infection. These should be treated in a radical manner and thoroughly eradicated. The number of cases of thyroidism de-

veloping following chronic and acute focal infection is so great that the evidence is strong for the theory of focal infection activating the gland. Tonsils, teeth, paranasal sinuses and the more remote gall bladders and appendices should not be overlooked.

The general management of the case is of major importance. Most patients will be ambulatory and remain in their homes. The environment should be free from anxieties and family cares and from false suggestions. The psychic control should be complete. The patient should be relieved from laborious duties and responsibility. If the patient can be hospitalized for a time the united improvement from rest and isolation will be of advantage. The diet should be nutritious. A glass of milk three or four times a day is desirable. The caloric intake must equal or exceed the output as nearly as possible.

Rest and diet may relieve entirely the mild cases, but after the metabolic rate has been brought to a certain point no amount of rest or drugs has any influence over the initial advantage. Aconite and quinine derivatives have no influence on the metabolism rate. They are like many other drugs which have been carried over from empirical medicine. Digitalis may be of value if there is decompensation from muscular failure and dilatation. It seems easier to introduce than to discard valueless drugs, yet there are many copied from one text-book to another.

#### SURGICAL TREATMENT

All that has been said applies to the general treatment of every case. Nothing more may be necessary in the mild forms of toxicity, but moderate, severe or repeating mild cases demand more effective treatment. Two methods of choice are given—surgery and roentgen treatment. The surgery of the thyroid has been widely adopted. The continental surgeons, especially Kocher and Mikulicz, prepared the way in the last century. The work of Halsted, Charles Mayo and Crile, in this country, has added a brilliant chapter to surgery. Since the adoption of the subtotal thyroidectomy technic the results have improved and the recurrences are fewer. This type of operation has raised the per cent of cure in one clinic (Mayo) twenty per cent. But there is still much uncertainty about the type of operation to choose and about when to operate. A master in this field of surgery has said that a successful operation only

begins the treatment. Until the time is ripe for operation the patient is either left to fret, or receives only that amount of improvement which rest can give. The destruction in the vital organs goes on. Surgery has a definite risk. Crile and Mayo may claim less than one per cent mortality from operation. This is in selected cases. Excellent surgeons under the best conditions admit five per cent. My own opinion is that the general run of good surgeons have a much higher mortality than these masters' statistics.

It is impossible to compare in a practical manner the per cent of cures by surgery and the roentgen ray. Neither speak the same language. Statistics are largely dominated by surgeons. Halsted gives 60 per cent cures in his 500 cases. Judd reporting on 121 cases six years after operation, concludes that 45 per cent were cured, 23 per cent practically cured. Haudek and Kiser give the failures in surgery on the continent as 10 to 27 per cent, from roentgen treatment 10 to 25 per cent. These failures are due to insufficient removal of gland by surgery or an insufficient roentgenization, and the presence of an abnormal pluriglandular constitution. They state that the recurrence after operation is 4.68 per cent, and after roentgen therapy it is the same. The fact is that few are completely cured. The clinical signs may disappear and the metabolism rate return to normal, but there remains a subnormal individual whose capacity in life is restricted. Instability and neurasthenic symptoms leave marks of the original disorder.

The method of choice must rest upon the risk involved, the selection of patients, and the economic condition of patients. General satisfaction of methods rests on clinical observation of results. The real development of roentgen therapy has only existed since 1914, when the Coolidge tube and standard equipment made it possible to accurately administer and reproduce dosage. Unfortunately sufficient time has not yet elapsed for roentgen statistics to show ultimate results. We can only examine those that are available and these are indeed hopeful.

The most outstanding reports come from the Massachusetts General Hospital. There for a half dozen years cases of hyperthyroidism have been studied from three viewpoints—the internist's, the surgeon's and roentgenologist's. The results are familiar to all. But, in comparing roentgen therapy and sur-

gery it was found that in the third year after treatment the end results were the same. In roentgen therapy the improvement was gradual and progressive, with surgery there was a sudden marked improvement and a subsequent relapse. The factor of rest was distinctly greater in the surgical group, yet no more ultimate benefit was secured. The chance of cure in exophthalmic goiter was no better with surgery than roentgen ray, and the risk was greater.

Surgeons offer objections to roentgen therapy:

1. That it does not produce permanent cures. Neither does surgery in a large per cent. Our statistics that are accumulating indicate that the cures about equal surgery when they are at all comparable.

2. That cardiovascular renal changes go on to the detriment of the patient. This is probably no more true in roentgen therapy than in surgery, for the surgeon selects his cases, does not operate on the crest or a rising metabolic curve.

3. That subsequent operations are more difficult. This objection is probably without foundation. It is denied by fair minded surgeons. Some others often use it for an excuse when their technique is poor. Adhesions, if present, are generally due to thyroiditis or perithyroiditis or previous surgery, especially ligations.

4. That the danger of hypothyroidism is great. Theoretically it should be as easy to carry out roentgenization as extirpation. Practically this danger rarely occurs. I found two or three cases in the literature where the metabolic rate had been reduced to an abnormal degree. Two of these took thyroid tablets and later returned to normal. It is well known that thyroid patients even untreated, may fluctuate below normal. In defense I also offer a patient's history treated for hyperthyroidism and extensive carcinoma of the thyroid gland. She has had short wave length therapy, three times the E. S. D. for treatment of the malignant goiter. It was given in desperate doses for over two years. It is now five years, the patient is alive, in good health and her basal metabolism is only ten minus.

#### ROENTGEN TREATMENT

The effects of roentgen rays are upon the thyroid gland. There is a slow degeneration of the parenchymatous tissue,



which is replaced by fibrous tissue if a sufficient number of radiations over a long period of time are employed. Since the gland is ductless there is no way to determine visually the reduction of the gland secretion, but there are good reasons to conclude that there is a diminution. Theoretically there is a field for roentgen therapy. Like surgery, it decreases the output of the gland. Analogy suggests this and clinical observation and the metabolic reading support the belief. The pathological effect of roentgen rays on tissue is controlled by the amount. Roentgenization can by judicious choice be carried to any logical point.

In the hands of an expert the dangers of roentgen treatment are small. Telangiectasis and atrophy of the skin seldom if ever occur if the dose is kept below an erythema skin dose. Prevention of untoward skin effects is by filtration and sufficient skin distance. Hypothyroidism is not a danger if the basal metabolism rate is recorded regularly.

The earlier the toxic goiter is treated the more prompt is the relief. Younger patients as a rule do better. A timely course of treatments may serve to prevent an established career of hyperthyroidism. Old cases of hyperthyroidism require a long rest after the roentgen treatment. There is no such thing as an innocent pathological goiter. These glands with any change whatever in them should be watched and treated whenever hyperthyroidism arises.

The first sign of improvement comes in about three or four weeks, when the patient reports improvement in the general bodily feelings. It is a frank statement admitted by the patient. Next will be noticed a fall in the pulse rate; then the weight begins to gain. Nervousness and insomnia improve. In about fifty per cent the exophthalmos eventually disappears. In most cases it improves. The thyroid enlargement is the last objective sign to go.

Its disappearance is frequent but on account of the pathology in the gland seldom complete. The end results depend entirely on the harm which has resulted to the human machine. Young individuals under thirty-five years show wonderful recuperative powers. The length of treatment must be guided entirely by the clinical symptoms and the metabolism rate.

The roentgenologist must have the full co-operation of the

patient. Many failures occur because some one else directs the case and the specialist is the technician. The one who directs the roentgen treatment must have full charge of the therapy. Either he is able to direct the entire management, or he is not fit to operate a switch in the treatment. It requires broad medical experience and high degree of expertness. This does not preclude a careful diagnostic study of the case, nor frequent consultations with any other expert. The patient's case must not be taken for a week, a month or for any limited time.

The indications for roentgen therapy may be grouped as follows:

1. All exophthalmic goiters not at too high a metabolic reading. The roentgen treatment may be cautiously started in those much too high for surgery.

2. To prepare for surgery by reducing the activity of the thyroid. Experience shows that few of them change to surgical treatment.

3. After surgical failure.

4. Adolescent goiter not responding to rest.

5. Adenomatous goiter with toxicity. Surgery may relieve the patient more quickly, but some of the satisfactory cases are in this class.

6. Carcinomatous degeneration after surgical removal accompanied by toxicity.

The contraindications are:

1. Colloid, cystic, fibrous and nodular goiter without toxicity.

2. Goiter causing marked pressure in the neck without symptoms.

3. Intrathoracic goiter.

Pfahler of Philadelphia has reported 200 cases of toxic goiter which he has treated with uniformly good results. He concludes that "Radiotherapy is the best form of treatment for toxic goiter," and the results are "equal to surgery."

Christie and Groover report 157 cases with results equal to surgery. They say, "The roentgen method is being used by an increasingly large number of internists, but very few surgeons have as yet been willing to give this method a sufficient trial."

weight and metabolism the changes which patients undergo while taking the roentgen treatment. It is definitely observed as the opinion based on this study, that the X-ray will accomplish as much as the surgery. It may require a longer time, but the results are just as good and the mortality is nil. Most types of toxic goiters are amenable to roentgen therapy. The contraindications are: (1) Colloid, cystic, fibrous and nodular goiter, without toxicity. (2) Goiter causing marked pressure with symptoms. (3) Intrathoracic goiter. The treatment of thyroid intoxication is major roentgenological work. Improvement is first noticed by a reduction of pulse rate, increase in weight, improvement in nervousness and insomnia. In about fifty per cent the exophthalmos will eventually disappear. In most cases it improves. In some it does not appear. Thyroid enlargement is one of the last objective signs to disappear. The end results depend entirely on the damage done, when the hyperthyroidism has disappeared. If degeneration of heart muscle and nephritis occur, improvement is often great, but a complete cure cannot be expected where these changes have occurred. All patients should have metabolism rate taken both for diagnostic purposes and from time to time in order to follow the treatment. The roentgenologist must follow his own cases. He must be capable of more than technical administration of the dose. He must have a broad knowledge of disease and an up-to-date conception of how to treat thyroid intoxication. Rest, isolation, psychic control, diet and eradication of focal infection are as much the duty of the roentgenologist to prescribe and follow up as is the administration of roentgen ray.

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# RADIUM THERAPY OF THYROID

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LINCOLN, ILL.

I have been treating goiter, in an experimental way, with radium for the past four years. During this time I treated every case that came under my observation, and this included practically every known type.

My results have been that a change was noticed in about forty-five per cent of the cases treated,—thirty-five per cent were regarded as cured and most of the cases treated were not benefited at all.

In treating thyroids, it is quite necessary to make a careful and accurate diagnosis,—for the thing of prime importance to the patient is the benefit to be obtained from such a treatment.

For this reason and for the interest of radiologists I have divided the different types of goiter into two main groups:

- (1) Cases with hyperthyroidism.
- (2) Cases without hyperthyroidism.
  - (a) Types of cases mentioned in the first group are:
    - Exophthalmic
    - Hyperthyroidism with goiter
    - Hyperthyroidism without goiter
  - (b) Those placed in the second group are:
    - Cystic
    - Colloid
    - Simple
    - Adolescent
    - Malignant
    - Intrathoracic

Cases in the first group may be treated with radium; those in the second group should never be. In other words, the percentage of cases that are to be benefited will be found only in the first group. Those in the second group not only receive no benefit, but the treatment may, indeed, prove harmful.

The benefit to be received by cases in the first group depends upon the ability of the radium rays to produce an inhibition or abolition of the secretory function of the gland or even the complete destruction of the secreting cells themselves. It is conclusive, then, that the treatment is indicated where there is an excessive secretion from the thyroid.

Cases in the second group in which radium is contraindicated,—a state of atrophy of the normal gland is produced, resulting in hypothyroidism. The size of the gland is much less affected in cases of this group than it is in cases of the first group.

The gland, at most, is not reduced completely after radiation, since the secretory cells are partially replaced by fibrous tissue, thus preventing a reduction to a normal sized gland. A reduction of two and one-half inches in the circumference of the neck is about the average.

While the metabolism test may mean little to the surgeon, I regard it as quite essential to the radiologist, as it serves as one of the many guides to a lessening in the degree of thyroid toxicosis that is gradually and continually taking place over the whole period of treatment,—usually three months. The metabolic rate at this time should be within the radius of normal. (No more than 15 plus or no less than 15 minus.)

The same is true of the blood picture. A hemoglobin, differential red and white blood count, is made, as a routine, at six different times during the treatment period of three months, and the change that takes place is most interesting.

As regards to the technique of application,—I block out the neck in four squares,—one over each lobe, one over the isthmus and one over the thymus. This makes four areas to treat. Usually 100 milligrams of radium is used. The radium element is encased in silver tubes 0.5 mm. wall thickness, and is further screened with 1.0 mm. of brass with two to three millimeters of rubber and mounted on a block of wood about an inch thick.

This is held in position with adhesive tape for four hours over each square. The procedure is the same for all cases, for the first treatment, and acts as a so-called "feeler" to determine the patient's susceptibility to radium rays. To those cases that are inclined to be radium immune. the dosage is relatively

increased over each lobe area. At least one-half lethal dose should be given at this time.

If there is no marked improvement as shown by the metabolism test and clinically, after three months' radiation, the case should be referred to the surgeon for operation. If the case is slightly improved, but not well, radiation should be continued at long intervals and the medical and hygienic treatment persisted in until the patient returns to normal.

#### ILLUSTRATIVE CASES

The cards I have with me represent 100 cases of the first group. I am going to pass them out so that you may see for yourself the very interesting picture they make on paper. Two sides of the history card is shown as in illustration. At the top of the front side is the name of the patient, address, case number, date, present history, previous history, diagnosis, previous treatment and by whom referred. The squares to the left represent the squares as they are blocked out on the neck and the space to the right is provided for a double check on the nurse in charge, for the time, milligram hours and the screening. The figures 1, 2, 3 represent the first, second and third treatments. Hours, marked at the top for each change of radium is given by a figure in each square. Figures on the reverse side correspond to the figure 1, 2, 3 on the front side and give you the changes in the blood picture at the time of each treatment.

Case No. 1—A woman of thirty-seven years, married and the mother of four children, the youngest being six years of age. About six years ago she noticed an enlargement of the thyroid and was later verified as a goiter by her family physician and since that time her symptoms gradually grew worse. She was extremely nervous, slept poorly and the mornings found her exhausted and disinclined to work. Her digestion was bad and she complained of choking spells. The usual eye symptoms were present.

Examination revealed a thyroid definitely enlarged, involving both lateral lobes, and measured seventeen inches in circumference. Her pulse rate 115, increased on slight exertion—metabolic rate was 72 plus. Her red cells numbered 3,172,000 whites 8,400. Hemoglobin 60%. I gave her a radiation every other day during a week's stay at the hospital, for three exposures for a total of 1500 milligram hours. She was then given

rest for thirty days and when she returned, the circumference of her neck was diminished two inches—metabolic rate was 45 plus and pulse 88. The choking spells had entirely disappeared and her nervousness and tachycardia were markedly improved. When she came back thirty days later, for her third treatment her metabolic rate was normal, her red count increased to 4,620,000. Her neck measurement was 14½ inches. The goiter had reduced in size until it was hardly noticeable and when I last heard from her in December 1923, practically three years later, she was in good health and her weight in that time increased twelve pounds.

Case No. 2.—This is a case of hyperthyroidism without goiter. A woman of thirty-one years and had previously had excellent health. About a year ago she developed nervousness, tachycardia and exophthalmus. She complained of headache along with her menses which were irregular. Loss of energy, sleeplessness, palpitation on slight exertion, tremor, digestive disturbance, profuse sweating at nights and gradual loss of weight. Her metabolic rate was 45 plus. While I do not depend entirely on the metabolism test, it is most essential to determine a diagnosis in many cases, especially the ones where many of the symptoms are masked and a plus metabolism will greatly assist in a diagnosis. In a case of this kind,—hyperthyroidism without goiter—attention to the teeth, tonsils and digestion is of prime importance. This patient was given 2000 mgh. in the course of a week's treatment. She went home for thirty days and when she returned she had made a gain of five pounds and was feeling very much improved. By the time she had taken her third radiation three months later she had gained fourteen pounds and had no complaints.

Case No. 3.—This is one of the exophthalmic goiter who give a history of influenza (intestinal type) in 1919, as did many others of the same type. She had the enlargement of the thyroid gland and protuberance of the eye balls along with the other recognized symptoms of severe hyperthyroidism. This was in 1922—three years following her attack of influenza. She began by having attacks of vomiting and was easily excited and nervous, with very rapid heart action on exertion. Her red count was 4,060,000 whites 11,600 hemoglobin 60%, metabolic rate 60 plus. In January, 1922, I gave her 2000 mgms. dur-



ing her week at the hospital, and when she returned for her last treatment in April, same year, I gave her 3000 mghs. She made a gain of twelve pounds since her first treatment in January. Protuberance of the eyes had entirely disappeared, nervousness, tremor, and palpitation were only recognizable on exertion. The last time I heard from her family physician she was still in excellent health.

Case record card illustrated below

### GENERAL REFERRING CARD

#### RADIUM DEPARTMENT

Name—Mrs. E. H. Case No. 812.

Address—Hartsburg, Illinois. Date, July 10, 1923.

Previous History—Childbirth, 1918. Influenza, 1918.

Present Condition—Local, both lateral lobes enlarged. General, nervousness, tachycardia, tremor.

Diagnosis—Clinical, exophthalmic goiter. Previous treatment, none. Referred by Dr. H. H.

Hours	Time	Mgh.	Screening
1.—4 4 4	8, 12, 4, 8	600	1 in. wood, 2 mm. lead, 1 rub.
4 4 4	8, 12, 4, 8	600	
2.—4 2 4	9, 1, 3, 7	500	
4 2 4	8, 12, 2, 6	500	
3.—6 6	8, 2, 8	600	
6 6	8, 2, 8	600	
		<u>3400</u>	

Age, 23; sex, female; weight, 118-133; height, 63; circ., 15-14-13; B. P., 112, 118, 118; B. Metabolism 7 or  $\frac{1}{2}$ , 70, 32, 12.

#### BLOOD

Date	Rbc.	Wbc.	Hgl.	Pl.	Ml.	Li.	Sl.	Ci.	E.	B.
July 11, 1923	3340000	15000	65	52	12	12	23	0.98	7	1%
	3715000	11600	65	83	..	6	8	0.88	.	3%
Aug. 16, 1923	4120000	10400	75	54	2	5	37	0.91	.	2%
	4160000	11200	75	71	4	6	16	0.91	.	3%
Oct. 15, 1923	4500000	7800	75	60	2	7	27	0.83	.	3%
	4620000	10000	75	82	2	5	11	0.81	.	2%

Pulse, 120-92-82.

## USE OF SEAWEED IN THE PREVENTION AND TREATMENT OF GOITER.

J. W. TURRENTINE, Ph.D.

WASHINGTON, D. C.

Iodine existing on the earth in forms that are mostly highly soluble in water, the bulk of it is to be found in the sea whither it has been deposited by drainage water. In the rocks which have their origins in the sea, some traces of iodine remain and in the drainage waters flowing over and through them. This small trace diminishes in concentration as the tops of drainage areas are approached, there the soils being more thoroughly leached out. The same is true of thin strata of soils overlying impermeable rocks. Thus, higher concentrations are found in soils and drainage waters occurring nearer the ocean, although here undoubtedly drainage is only one factor as the supply of iodine is prevented from disappearing there through additions gained from sea spray blown inland.

Iodine is sea water, as stated by Hayhurst in his comprehensive article, "The Present-Day Sources of Common Salt in Relation to Public Health and Especially to Iodine Scarcity and Goiter,"\* quoting Molinari, exists to the extent of 0.01 gm. iodine (calculated to NaI) per liter, and, quoting Gautier, occurs in three forms, for the most part in organic combinations dissolved in the sea water, a small portion also in the organic form, in sea organisms, and a further small portion in the inorganic form, but occurring only at great depths.

When land deposits of sodium chloride were developed through the desiccation of sea water and the crystallization of sea salts, iodine salts were not deposited, both because of their extreme solubility and likewise their extremely low concentration in sea water as compared with that of the salts deposited. So, even here, where the desiccated products of sea water are found in enormous quantities and in great varieties, iodine is almost entirely absent; and as pointed out by Hayhurst, in preparing these salines for human use, both in the manufacture of

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\* J. Am. Med. Assn. 78, 15 (Jan. 7, 1922).

salt for dietary purpose and other salines for fertilizer purposes, the salts are refined and impurities, particularly the more soluble ones, such as iodine salts, are carefully and completely eliminated. Thus from soils where they would not be expected and from salines where they would be, iodine salts are thoroughly removed.

Small and varying amounts of iodine are found in plants, and in the animals feeding upon them. The occurrence of iodine in food materials has been studied by Forbes and Beegle,<sup>†</sup> especially from the point of view of goiter. While they find that there is not a sufficient divergence of iodine content of the foods grown in goitrous and non-goitrous regions to account for the varying incidence of that disease, they point out "the smallness of the proportion of our food products which contain iodine, the minute quantities in which iodine is ordinarily found and the haphazard nature of its distribution."

Just as the soils occurring near the ocean contain more iodine, so it is to be expected that the plants growing thereon will likewise and it is shown by Hunter and Simpson, as stated by McCarrison, that the thyroids of sheep grazing near the ocean contain more iodine than those grazing inland.

But the occurrence of iodine to a remarkable degree in plants is confined to those that grow in the sea. In certain sea plants the iodine content, as will be shown, is phenomenal.

The foregoing suffices to show the intimate manner in which the normal supply of iodine for the metabolic use of the human body is linked with the sea. And in this connection it may be suggested that in this fact is found a bio-chemical bit of evidence in support of the theory of evolution, or at least that part which hypothesizes a marine origin of animal life. Our early metabolism being established on the basis of chemical elements available or always present in that medium of existence, it has not been possible yet to evolve a new system of life processes which can do without these elements. McClendon<sup>\*</sup> voices the same idea in a different manner when he says:

"It has been considered by some biologists and chemists that living matter originated in the sea and the elements of living matter correspond to those found in the sea water. We might

<sup>†</sup> Bull. 293, Ohio Agr. Expt. Sta.

<sup>\*</sup> "Are Iodines Food?" Science 55, 1423 (April 7, 1922).

look, therefore, to the composition of sea water for the elements we should expect to find in living matter."

He accordingly, recognizing the general iodine deficiency in the diet of the average man and appraising the possible value of the other ingredients of sea water, advocates the use of unrefined sea salt as a condiment or diet amendment and shows how it may be prepared in a non-hygroscopic form not disagreeable to the taste.<sup>†</sup> In this he is ably supported by Hayhurst who says—"Of the dependable sources of iodine in nature—sea air, sea food and sea water—it is to sea water \* \* \* that inland dwellers should look. This substitution would appear to offer a complete solution to the iodine deficiency problem, if nothing else, while evidence would tend to show that other constituents of sea water have an undoubted place in the economy of the higher animal organism, perhaps to the extent of precluding some diseases which are likewise, possibly, of a deficiency type."

Entirely in support of this evident close relationship between goiter and the sea are the goiter maps based on the observations of the draft boards during the last war.\* The data on which they are drawn show that the incidence of simple goiter varies from 1.02 among men residing near the sea to 17.55 among those from inland regions. They illustrate the increasing incidence as tops of drainage areas, the Appalachians, the Great Lakes regions, and the Rocky Mountain regions, particularly the Pacific Northwest, are approached.

In entire accord with these data are the striking observations of McClendon showing a parallelism between goiter incidence and the absence of iodine from drinking water.

It will be noted, by a comparison of the respective maps for simple goiter and exophthalmic goiter, that there is a remarkable coincidence in proportional incidence. While there is no etiologic connection so far recognized between these two forms of thyroid derangement, here is a phenomenon that demands explanation. The two are regarded by some as opposites of each other, yet both are derangements of the thyroid gland and both exhibit a deficiency of iodine in the gland. They occur side by side, the general conditions that induce one—so far as these condi-

<sup>†</sup> See also a later article by McClendon, "Simple Goiter as a Result of Iodine Deficiency," J. A. M. A., 80 (1923), 600.

\* Defects of Drafted Men. War Dept. Publication.

tions are understood—inducing the other. Both are the result of hyperactivity. In one the hyperactivity takes the form of hyperplasia, while in the other, of excessive secretion. Are they the opposites of each other, or are they different manifestations of the same thing? One is demonstrably the result of iodine deficiency. Can we escape the conclusion that the other is also?

#### LACK OF IODINE IN NORMAL DIET

The modern diet is made up of highly refined materials. Seeds constitute most of it. These, in their normal state, in addition to materials of great value as sources of energy, contain many of the mineral elements and compounds essential to animal life and growth. But in most cases they are refined to the point where the latter are eliminated. As a result they are not able to sustain life; and it has been shown that animals fed on certain of them exclusively perish more quickly than do those entirely without food. The excessive use of refined foods leads to deficiency diseases. In this category are those diseases induced by a deficiency in the vitamins, now receiving most marked attention, and of a joint deficiency in vitamins and other things, as a lime-vitamin deficiency; amino acid deficiencies, as in pellagra and deficiencies in the various inorganic or mineral elements of food less well recognized. There are some fourteen elements which at present are regarded as essential to the economy of the human body, which are calcium, magnesium, iron, sodium, potassium, chlorine, iodine, fluorine, phosphorus, sulphur, carbon, hydrogen, oxygen, nitrogen. Very conspicuous in point of number (though not of quantity) are the so-called mineral elements. Contained largely in the skins and husks of the common food materials they are generally eliminated. Over refinement in food manufacture accordingly deprives us of these essential elements which under less artificial conditions would be a natural part of our diet. No automatic method is provided for supplying these materials of great importance in every case, but of the greatest importance in connection with the feeding of the young. The diseases of the bones in growing children as a result of deficiencies, particularly of calcium and phosphorus, are well recognized. Less attention is paid to the frailty and inadequacy of the teeth as a result probably of similar causes.

Together with deficiencies of the many commoner elements, there occurs of course, an even more marked deficiency of iodine. The occurrence of iodine in food materials is well shown by the elaborate research of Forbes and Beegle as summarized in the following table:

	Total number of samples	Number containing iodine
Animal products .....	35	13
Cereals .....	378	60
Fruits .....	34	5
Garden vegetables and root crops.....	131	39
Hays, silage and forage crops.....	205	50
Leguminous seeds .....	32	11
Manufactured foods, and milling and manufac- tory by-products .....	25	13
Nuts .....	7	0
Sea weeds .....	2	2
Spices, condiments and stimulants.....	27	2
Water .....	2	2

This summary shows that the various groups analyzed, in the order of the increasing frequency of iodine occurrence, may be arranged as follows: (1) Nuts; (2) spices, condiments and stimulants; (3) fruits; (4) cereals; (5) hogs, silage and forage crops; (6) garden vegetables and root crops; (7) leguminous seeds; (8) animal products; and (9) manufactured foods and milling and manufacturing by-products. "Among the cereals iodine was found as an uncommon constituent, usually in traces only."

#### METHOD OF SUPPLYING IODINE TO THE DIET

As a source of iodine for human metabolism it is obvious one must look to the sea, the great storehouse of that essential element and choose that method of securing the requisite quantity in the manner which most readily coincides with one's already established dietary habits. Sea foods might well become a more common article of diet but at the present cost for preservation and transportation do not reach the majority of people. Sea salt is not a commodity at present obtainable on the market but its wide introduction as a condiment would be of great benefit to the human race. A logical and from many points of view an ideal conveyor of all these essential elements are the kelps, the larger sea weeds of the brown algae group.

#### COMPOSITION OF KELP

In recent years, and on occasions in earlier years, a great deal of study has been devoted to the composition of kelp. The

literature is replete with references to these investigations. Kelps have been studied from the point of view of their utilization as foods, and as carriers of inorganic salts and of iodine.\* The different species vary in chemical composition, quantitatively rather than qualitatively. Most of the work of recent years has been devoted to the single giant kelp of the Pacific, the *Macrocystis Pyrifera*, which has been the main basis of the extensive investigations of the U. S. Department of Agriculture. Its composition is more thoroughly understood perhaps than that of any other kelp.

The composition of this kelp has been studied to determine its water, organic, inorganic, nitrogen, protein, sugar and fat content. It is tremendously complex, being made up of a great variety of organic and inorganic compounds and of organic compounds containing and probably combined with mineral elements. In organic combinations are parts at least of the iodine, the phosphorus and the sulfur. All of them are held in varying degree in colloidal suspension in the plant.

A great many analyses of *Macrocystis Pyrifera* have been made in State and Federal laboratories, mostly to determine its inorganic content. These show on the average: Potassium chloride, 22%, sodium chloride 10% and water-insoluble ingredients, 7% (on the dry basis). Entering into this total of 37% inorganic material are: Calcium, 4.96%; magnesium 2.24%; sodium, 10.52%; potassium, 29.46%; iron and aluminum oxides, 0.43%; chlorine, 34.93%; sulfur (calculated to  $\text{SO}_3$ ), 7.92%;  $\text{CO}_2$ , 4.44%; phosphorus (calculated to  $\text{PO}_4$ ), 2.30%. All of the kelps contain iodine, though some only a trace.

The iodine content of this species is phenomenal. Of 29 samples analyzed for iodine, an average content of 0.26% was shown, with a maximum of 0.41% and a minimum of 0.17%.

The organic constituents are of a widely varying nature; many of them partake of the nature of sugars. One finds pentosans, galactans, levulans, methyl pentosans and "Alginic" acid.†

Kelps have been shown to be a source also of vitamins. The remarkable vitamin content of certain fish oils, notably codfish

\* Turrentine, "Potash from Kelp" (I-VII). J. Ind. Eng. Chem., Vol. 11 (1919) to Vol. 15 (1923).

† Hoagland and Lieb, "The Complex Carbohydrates and Forms of Sulfur in Marine Algae of the Pacific Coast." J. Biol. Chem. 23, No. 1, Nov., 1915.

oil, has an ultimate origin in the vegetable growths of the sea. The presence of vitamins in various sea plants has been demonstrated by Drummond.

From the foregoing it is evident that kelp contains the principal ingredients of sea water, and has stored them up within itself in even greater concentration than most of them exist in sea water. This is particularly true of potash and of iodine. What other elements are present in kelp likewise present in sea water remains to be shown when specific researches are carried on to demonstrate their presence or absence. It appears logical to assume that practically all of the elements found in sea water are likewise to be found in kelp, since its adsorptive capacity is such as probably to make impossible the exclusion of any one of them. It appears, therefore, to be an ideal concentration of the desirable elements of sea water with the relatively marked elimination of the most common and least valuable—common salt.

Of the fourteen elements above listed as essential to the proper metabolic functions of the human body, thirteen are definitely known to be present in kelp and the fourteenth, fluorine, doubtless will be found when it is looked for.

#### DESIRABILITY OF KELP AS A DIET AMENDMENT

As a conveyor to the diet of the essential mineral elements, kelp seems to possess many ideal characteristics. Its composition establishes it as a carrier of iodine of remarkable properties—a high content of iodine together with a great assortment of other useful elements. The source of raw material is abundant. Methods have now been perfected whereby the kelp may be so processed that its colloidal parts remain unimpaired and its mineral content unreduced. When so processed it is a carrier of these elements and compounds in a natural, vegetable colloidal suspension, from which or through which they may be taken up by digestive processes just as they would be if they were made available as normal, natural parts or constituents of the usual articles of diet. Being highly concentrated in these, preparations may be made in condensed forms so that transportation costs are reduced to a minimum and the convenience wherewith they may be added to the diet is greatly enhanced. For the latter purpose they may take a variety of forms, suitable for addi-



tion to the diet of people of varying ages and dietary habits. It is important that kelp to be used in connection with goiter be employed as a preventive as well as a cure, that it be added to the diet of the young and to all of those approaching or experiencing life crises. It is contended by some that its addition to the diet should be made a part of a culinary or dietary routine and not left to chance or the caprices of the memory. On the other hand, the disciplinary and educative advantage to be had from consciously taking as a diet amendment a concentrate of mineral matter in tablet form must not be overlooked. Being abundant, cheap and conveniently acquired and stored, it should be made available for all people of all lands. Through its instrumentality, as a carrier of iodine and other desirable elements, not only goiter but any other disease depending on related deficiencies may be eradicated.

The present methods of combatting goiter by the administration of sodium or potassium iodide or thyroxin, leave much to be desired. The administering of iodides, as for example, dissolved in the drinking water of a school, while efficacious in furnishing the iodine requirements of the pupils, results in uneven dosage, though rarely in such an excess dosage as to cause symptoms of iodine excess; yet Bircher\* describes the practice as causing harm. Their use should be supplanted by that of iodine carriers which cannot induce idoism.

The administration of thyroxin, the iodine-carrying constituent and an active principle of the secretions of the thyroid gland, is sometimes found efficacious in cases where the gland fails to supply the required amount of that compound. As this is probably only one of the normal products of secretion of that gland if given alone it may not and often does not meet the requirements of the case. Furthermore, to determine the proper dosage it is necessary to know something of the deficiency to be met. So far no technique has been generally adopted for accomplishing this purpose, so the proper dosage is frequently a matter of guess and an overdose may cause symptoms as serious as those it is sought to alleviate. In other words, the use of thyroxin and other thyroid preparations is not based on any thorough understanding of the secretions of the thyroid gland or their functions, nor of the amount required by the system.

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\* Schweiz. Med. Wschr., 52, 713 (1922).

What the situation requires is iodine in a form as closely as possible approximating the natural form in which that element is normally taken into the body. Salts of iodine radically fail to meet this requirement. They are very soluble and therefore are able to overcome the natural metabolic balance of the body solutions and thus rapidly force their way into the circulation and out.

Depending on an infrequent administration of iodine salts sets up a feast-or-famine state of affairs and in no sense simulates that constant and steady supply which is the normal method of meeting the body requirements. However, it should be emphasized, this method of combatting goiter is infinitely to be preferred to no effort at all.

It is preferable that the body be permitted to secure its iodine from some natural, vegetable carrier of iodine, by natural digestive processes of selection and elimination through a prolonged digestive period rather than from some chemical, highly soluble and of high penetrative powers, against which the natural protective and defensive agencies of the body are not able to prevail.

Absorption is necessarily different where equilibrium is to be maintained between two absorbing colloids than where a highly soluble salt on the one hand and a colloid on the other are involved. Thus to administer iodine as a suspension in a colloidal, vegetable extract and permit equilibrium to come about between it and the colloids of the digestive system is radically different from the conditions brought about where a highly soluble salt in solution is admitted as one element of the equilibrium.

It must be remembered that iodine is administered in goiter not on account of any physiological action it may have as such, but quite on the contrary. Its physiological action—as exhibited by iodism, for example—is exactly what one desires to avoid. Iodine is given merely to furnish raw material to the thyroid wherewith to manufacture essential secretions. The situation demands physiologically inactive iodine, insofar as such is attainable.

The presence within kelp of other highly soluble halides makes it possible that the chemical and physiological activity of any portion of the iodine present as or converted into iodide

may be "buffered" and depressed. This would tend to function as an automatic protection against an unbalanced dosage and to assist in the maintenance of the proper balance.

#### CLINICAL RESULTS

Time enough has not yet elapsed since the inception of the idea to use sea plants for the prevention of goiter to make possible a demonstration of the soundness of that proposal. In the therapeutic field, however, very interesting results have been obtained, such, it appears, being obtainable in very short periods of time.

The iodine-carrying constituents of sea plants have been processed into concentrates which, in the form of compressed tablets, have been administered to patients of various ages and victims of thyroid derangement of a variety of forms. Conspicuous among these have been patients who have been kept under constant medical supervision and whose progress has been carefully noted and recorded. Others have had only occasional observation. Without presenting the details of these cases, it may be said the results observed have in the great majority of instances been favorable. The nervous disorders characteristic of hyperthyroidism have responded more readily. "Simple" goiters of long standing and in cases of people of more advanced years have been the slowest to respond.

Among the results observed have been the immediate restoration of the metabolic ratio to the normal and the prompt subsidence of tachycardia and tremor. Cerebral stimulation has become less marked. Hyperplasia has decreased and in instances apparently has entirely disappeared. In the single instance under observation where a serious functional derangement of the ovaries existed, this has been corrected. In all the cases where frequent periods of excitement (violent insanity) occurred,—requiring the confinement of the patient in an institution—these have entirely ceased to appear. In the majority of cases the patient has expressed a marked increase in a sense of comfort, strength, and generally improved health and ability to work without fatigue, and in no instance has there been observed any unfavorable result.

The already considerable and rapidly growing mass of clinical data at hand is not yet sufficient in point of number of cases observed to justify sweeping generalization. At the same

time their positive nature, the number of respects in which improvement has been observed and the advanced stage of some of the cases where benefit has been recorded would appear to justify the belief that the form of iodine and its concomitant mineral elements here used represent a valuable therapeutic agent for use in goiter, particularly where the necessity for an operation does not exist or where the patient is undergoing treatment in preparation for an operation, and probably for the prevention of the recurrence of thyroid derangement following operations.

# SURGERY OF THE THYROID

JOSEPH L. DE COURCY

CINCINNATI, OHIO

There are three great questions or problems that confront the medical profession, and laity as well, today. These problems are:

Cancer  
Tuberculosis  
and  
Goiter

Concerning the first, very little is known; as to the second, great strides have been made.

Goiter, the third great problem, is not as complex to the medical profession as the other two, for I believe we have in a great measure found some of the underlying causes of goiter and a successful way of combating it in the early stages before the operation period is reached.

As this meeting is concerned with the study of goiter, I would like to approach it briefly from several angles:

First—Rapid increase of endemic or simple goiter in the United States.

Second—Iodine as a possible prophylaxis.

Third—Fatigue as a cause of goiter.

a. Overwork in adults.

b. Too strenuous exercise in schools, especially among girls.

Fourth—Surgery.

So far the best solution for caring for advanced goiter.

From the best sources of information, we gather that endemic goiter is on the increase in Ohio and other regions that are located in what is known as the goiter belt. Many causes have been advanced in regard to this increase. Chief among these causes as given is fatigue, or overwork. It is therefore important that those who specialize in goiter should investigate all the possible causes and remedies for the condition that is so prevalent in our own locality.

Iodine as a factor in the control of goiter has come into prominence within the last five or six years. The use of iodine as a preventative is not new, for we are told that the Greeks in 2000 B. C. knowingly employed iodine in the treatment of goiter. (Kimball, in *American Journal of Public Health*, 1923.)

In 1820 Coidet used it as a treatment for goiter, and Bauman in 1895 recognized that the active principle of the thyroid is a very stable compound of iodine. It was proven by Marine and Lenhart that goiter cannot be produced in an animal if the thyroid is kept saturated with iodine; while if an animal is deprived of iodine, the thyroid will start to enlarge as soon as the iodine content gets below one-tenth of one per cent of the total amount of dead gland tissue. (Kimball, in *American Journal of Public Health*.)

In 1918 work was begun in schools of Zurich. It was found in some schools 100 per cent of children were goiterous. Because of the high incidence of goiter in that region in both sexes the prophylactic treatment was given both boys and girls. The suggestion was accepted that a few milligrams of iodine given weekly throughout the year would produce optimum effects. Instead of sodium iodine the Zurich authorities employed an organic iodid which is non-hygroscopic, almost tasteless and very stable—a vegetable fatty compound which is combined with chocolate and made into tablets—each containing 5 milligrams of iodine.

This method has been employed in St. Gallen, Berne and Zurich for more than three years with even more striking results than those obtained in this country.

This work has also been extended in this country and in at least a dozen cities in Michigan, Ohio and Wisconsin some effort is being made to carry out this work in public schools.

It is possible, therefore, that in endemic goiter districts, if every woman would keep her thyroid saturated with iodine during every pregnancy, she would not develop goiter, nor would there be any tendency toward goiter formation in the thyroid of the child. This would save two of the goiter periods in the life of any individual. If every girl would keep her thyroid saturated with iodine during adolescence—from 11 to 16, inclusive—none would develop goiter. As this work is still in the experimental stage, and as the time covered by these

observations is comparatively short, we must await further results, and in the meantime we should not lose track of other possible causes of goiter, principally focal infections and fatigue.

Turning from preventive treatment of the growth of goiter, I would like to discuss fatigue as a cause of goiter.

In taking the histories and examining a large number of goiter patients it has been impressed upon me that "fatigue" plays an undisputable rôle in the causation of goiter. In almost every instance, the patient with a goiter has undergone a stress in life which has carried her beyond her normal "zone of endurance," whether this stress be mental or physical. For instance, we see goiter commonly in the lower class of farmers, women who have raised large families on meager incomes, teachers and students, especially teachers of the various religious orders, who together with their work have little or no recreation. Frequently we see nurses in training suddenly develop exophthalmic goiter.

The preponderance of goiter in women can be accounted for by a lower point of normal endurance than that found in men. It is a well known fact also that many men develop goiter when suddenly thrown under the stress of army life. Just how fatigue would affect the thyroid it is hard to conjecture, whether it is due to an acidosis, or whether it is a gradually increased call upon the thyroid secretion. I believe that a similar condition exists in the prostate gland which develops in adenoma possibly from over-use. The most logical way of accounting for the formation of an adenoma is a compensatory increase in cells in order to make up an existing deficiency. Every person has a normal zone of endurance which is individualistic in its characteristics. This zone may be decreased or increased by various external or internal conditions; externally by our mode of living, excesses, abuses, atmospheric conditions, hygienic conditions, etc.; internally by gradual toxemia from the intestinal canal, mental strain, focal infection, fevers, etc. The zone may be decreased or increased normally only by changes gradually induced, and has a limit. An example may be the athlete who must train slowly if his endurance is to be increased. The glands of internal secretion act normally, within the zone of endurance; let this zone be exceeded or fall below the normal limit, however, and one

of several changes must take place. If the zone has been exceeded suddenly, then the glands, whichever they may be, are activated to sudden hypersecretion, and if this gland be the thyroid, then hyperthyroidism suddenly develops. I recall the case of a clerk who, desiring an outdoor position, began driving an ice-cream route wagon, which demands heavy lifting and which pays the driver by the percentage of sales, in order to encourage abnormal energy. This man, after two weeks' work, suddenly developed an exophthalmic goiter, which disappeared after his return to his former position. If, on the other hand, the zone has been exceeded gradually, then the changes in the gland are apt to be by a gradual increase of cellular elements and we have an adenoma develop.

Once pathology develops in the thyroid gland, there is a possibility of its tendency being transferred from mother or father to daughter or son. That certain atmospheric, climatic and material differences are more inducive to fatigue than others, would possibly account for the geographic distribution of goiter. I am not aware of the percentage of goiter in the Negro, but I believe it to be comparatively small, possibly because of their lazy dispositions. This is true also of persons residing in the Southern climates. In cases of lung tuberculosis, especially in the ambulatory type, we frequently see signs of hyperthyroidism. When these patients are placed at rest for a while, these symptoms disappear. What probably happens is that the tuberculosis has narrowed the patient's zone of endurance and when she persists in doing the work which she was able to do when well, she exceeds her zone, and the thyroid gland is activated to hypersecretion.

Those of us who have given a great amount of time and study to goiter recognize that an ounce of prevention is worth a pound of cure. But in a large number of the goiter cases that we have to deal with, advanced goiter has developed before consulting a physician or surgeon. For these, surgery seems to offer the only solution.

It has been observed for years past that surgery, with the etiology at hand, offers the most logical treatment for this type of case. Its principal objections, however, have been its immediate mortality rate, its resultant scar, a not infrequent temporary loss of voice, or hoarseness, or an interference with



the singing voice, a resultant myxoedema, or a recurring enlargement of the remaining thyroid tissue and lack of a 100 per cent cure. These objections, which loomed so large a few years back, have, however, been eliminated one by one, until at present the results attending thyroid surgery are equal if not slightly better than the results attending any other type of surgery.

The mortality rate has been gradually reduced, until at present we have a report from the Mayo clinic giving a mortality of less than 2 per cent in over 1,900 consecutive operations, while Crile reports five deaths in 500 operations, a mortality of 1 per cent, and at the same time a consecutive series of 331 thyroidectomies and 145 ligations with no deaths.

In our own series of 1,245 thyroidectomies and 253 ligations, or 1,498 cases in all, we have had 21 deaths, a mortality rate of approximately  $1\frac{1}{2}$  per cent. In this series only a few cases were refused operation, many of which were "in extremis" when they entered the hospital. We have classed as operative deaths all cases which died while at the hospital. Fifteen of these deaths were following bilateral resections, 5 were following unilateral resections, and 1 following simple single ligation. Of the bilateral resections which died, two died within forty-eight hours from acute hyperthyroidism, and one on the ninth day from myocardial insufficiency, the reaction following operation having been comparatively slight. Of the 5 deaths following unilateral lobectomy, one died two hours following operation; the exact cause was never determined, although collapse of the trachea was suspected; another died seven days following operation from cardio-renal insufficiency. This patient had lost fifty pounds within three months preceding operation. Two ligations had preceded his lobectomy. Since this death I have placed a bad prognosis upon every thyroid case presenting a rapid loss of weight. The death which occurred following single ligation was due to acute hyperthyroidism, death occurring on the third day following. In other words, counting only immediate operative deaths, our mortality would figure about 1 per cent. In the last 500 cases, we have not had a death from acute hyperthyroidism, due largely to improved judgment.

The resultant scar is scarcely noticeable and frequently

imperceptible when the incision is properly placed and properly closed. The incision which we use now is in the lower crease of the neck, about one-half inch above the sternum. We have found that because of the looseness of the skin of the neck this incision gives a better and less noticeable scar than when placed in a lower position. We close the incision by placing a very fine catgut suture in the platysma and use small skin-clips for the skin. We remove these clips on the third day following operation, or approximately seventy-two hours. We use a small strip of gauze saturated with vaseline, which is brought out in the center of the wound, and leave the drainage in place for 24 hours. We have found that even when an infection results it can be satisfactorily handled through this opening without separating the incision. If the infection becomes alarming, however, which is very rare, then the incision may be opened.

Temporary loss of voice or hoarseness is not an uncommon sequel of thyroid operations, but concerns us chiefly because of the temporary discomfort. Permanent aphonia has only been reported in the literature as occurring twice. In one of our patients the voice entirely disappeared for four months, then gradually returned to normal. In six the voice was reduced to a whisper for three to five months, then gradually returned to normal. In 5 per cent of all bilateral resections a tracheitis and laryngitis resulted, many of which persisted for four to six weeks. Lately we have discontinued stripping the entire isthmus from the trachea, but are leaving a small strip of gland overlying and the inflammation following has neither been so severe nor so frequent. Interference with the voice following operation is frequently due to a combined laryngitis and tracheitis rather than to injury to the recurrent nerves. Another technical point which may be mentioned in order to avoid injury to the nerves is to wipe the capsule away from the gland with gauze dissection, thereby carrying the nerves away from the field of operation. Resultant attachment of the scar to the trachea not infrequently interferes with the singing voice. To avoid this we divide the sternothyroid and hyoid muscles at least one inch above the skin incision.

Evidence of myxoedema following bilateral resection occurred in only three or four cases, and this was immediately and permanently relieved by a two months' course of thyroid

extract, together with our routine post-operative régime, dependent upon the cause, of which we speak later.

Recurring enlargement of the remaining tissue is apt to occur, especially following bilateral resections for colloid goiter. This speaks for, and evidently is, a compensatory recurrence. Crile gives iodine in these cases, basing its administration upon the control of endemic goiter with iodine; but we go farther and attempt to eliminate the cause of the original enlargement whenever possible. We have found that this type of goiter especially is prone to follow any elements which tend to exceed our normal zone of endurance.

Surgery's chief criticism in thyroid surgery has resulted because we occasionally find cases which are not benefited; in other words, surgery is not a 100 per cent cure in thyrotoxicosis. This is so, I believe, because surgery, up to the present, has not been founded upon a definite etiology. In order to effect a complete cure, therefore, it is not sufficient to merely remove the pathology, but we must also in our post-operative treatment attempt to eliminate the primary cause of the pathology. And this is true in other surgery as well. With this in view, we have attempted to establish a post-operative régime, whenever possible, which will tend to prevent a recurrence of the goiter or its symptoms and thereby affect a cure.

The discussion of the various phases of the etiology of goiter which we have given lends itself admirably to a logical post-operative régime, keeping the patient well within her "normal zone of endurance," insisting upon a certain amount of relaxation and recreation, changing occupation when thought advisable, overcoming constipation, etc.

With the above surgical interference and post-operative régime, we have estimated an improvement in all cases, consistent with a normal endurance in fully 90 per cent of cases.

## DIAGNOSTIC ENDOCRINE CLINIC

DR. WM. ENGELBACH

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The immense amount of rich material that has been collected for this clinic is a marked complement to the program committee of this Association. More than twenty interesting and rare endocrine disorders have presented themselves for diagnosis. Of this number only thirteen were selected, and in order to economize your time these have been arranged for demonstration in groups.

The fact that so much material could be accumulated so easily and quickly demonstrates two very important facts concerning the necessity of more intensive study not only of the thyroid, but of the ductless gland disorders in general. The first and most important fact is that these internal secretory diseases are so common that their incidence is as marked as diseases of any other system. Second, there is a great demand and a very pressing need for every stimulus that can be brought to bear upon the study of and research in the disorders of the ductless glands. It is just here that this Association, which really should be a part of the International Association for the Study of Internal Secretions, has its most purposeful field. For many years we have been educated through the work of the surgeon in the anomalous functions of the thyroid. With the exception of this *one* gland, however, I believe that the real importance and prevalence of endocrine disorders are not appreciated. In order to demonstrate the frequency of ductless gland disorders as compared with diseases of other systems of the body, it will be necessary for me to quote from personal experience. In conducting a practice of internal medicine which is not limited to any particular field (for we believe that it would be ridiculous to attempt to make a specialty of the internal secretions), we have found, during the last five years, that there were as many disorders of the ductless glands presenting themselves for diagnosis at an internal medicine clinic as there were diseases of any other one system. That is, there are actually

as many endocrine disorders as there are lesions of the cardiovascular system, the respiratory system, the gastro-intestinal system, the genito-urinary system, or the musculo-osseous system. We are sure that this prevalence of internal secretory disorders is not limited to one section of the Middle West. On the contrary, the condition prevails to a greater or lesser degree throughout the entire country. Yet it is difficult to impress this fact upon the medical profession, who believe (1) that the ductless gland disorders are very rare, (2) that they are very difficult to diagnose, and (3) that when an occasional case is diagnosed the treatment is of little avail. This medical idea exists, I am sure, because of the lack of knowledge concerning the endocrines in general, and this lack of knowledge is due to the fact that there has been very little taught in the medical schools of this country on ductless gland disorders. There are only two universities in the United States which give systematized courses in internal secretions, the University of Pennsylvania, which has dedicated a department in honor of Professor C. E. de M. Sajous, and the St. Louis University School of Medicine.

This is a field which should be presented more directly to the layman on account of the fact that it deals with the basic principles of growth and development of the individual. Particularly necessary is the knowledge of these important functions during the early life, when the internal secretions have such an influence in developing the nervous system. We have had public campaigns of education on other diseases, such as syphilis, tuberculosis, cancer, and venereal disease, all of which pertain to acquired diseases of the adult,—in many cases late adult life, for which the patient is personally responsible after he has arrived at a mature age when he should be independent and able to exercise the ordinary precautions against advanced and unfavorable conditions resulting from neglected early treatment. The endocrine disorders, however, affecting the helpless infant and dependent child, producing such marked retardation in the infantile and juvenile growth and development, with subsequent mental incompetency and delinquency, have been neglected entirely. The medical profession as well as the laymen have indifferently and inactively allowed thousands of children to pass through this abnormal stage of maldevelopment and immature growth into an incompetent, defective or criminal.

For this reason every city and state of the Union have on their hands in almshouses, sanitariums, and asylums hundreds of thousands of these individuals, who become a tremendous charge upon the state, as well as tragic afflictions to their families and relatives.

As has been stated before, there has been an unusual amount of work done upon thyroid disorders, but ninety per cent of this has been devoted to the hypersecretion of the thyroid. There has been comparatively little advanced in the *early diagnosis and treatment of hypothyroidism*, and until recently an insignificant amount of work has been devoted to the *other glands of internal secretion*. Yet when we begin to study these subjects intensively, we are surprised to discover that there are as many pituitary and gonadal disorders as there are thyroid disorders, and probably if more were known about disorders of the adrenals, thymus, and other glands, we should be startled to discover that they also are as prevalent as the thyroid disorders. For this reason, while this Association is devoting its efforts entirely to the study of goiter, I believe it will serve a good purpose, because no one can earnestly take up the study of one of these glands without becoming intensely fascinated by and carried along to the study of the interrelationships of the ductless glands.

#### GROUP I, BILOBAR INSUFFICIENCY OF THE HYPOPHYSIS

Owing to the large material we have to demonstrate in a short time, it will be necessary to speak only of the general diagnostic signs which can be objectively shown. Neighborhood signs or special studies devoted to the basal metabolism, blood chemistry, etc., cannot be given consideration in these cases. After all, it is the general hormonal signs presenting themselves so objectively which are the most important diagnostic signs. A suspect diagnosis can be made in many of these cases from a rather casual examination and cursory history.

In the first group we will show three cases of juvenile adiposity, which is one of the early classical signs of insufficiency of the posterior lobe of the pituitary gland in the preadolescent age. It can be seen that all these children are very much overweight, without taking time to weigh them or compare their weights with the standard for age and height. For instance. Case No. 1

is a boy aged thirteen weighing over 160 lbs.; Case No. 2 a girl aged ten weighing 205 lbs.; and Case No. 3, a male aged fourteen weighing 230 lbs. It might be well to stop just long enough to discuss adiposity in general at this time. Our monograph on "Endocrine Adiposity" appearing in the Clinics of North America, St. Louis Number, Vol. 6, No. 1, 1922, gave our ideas with regard to the diagnostic value of the age incidence of adiposity. In this article we stated that (1) an adiposity occurring at birth (a weight of over 8 lbs.) means in seventy per cent of the cases, excluding birth anomalies, moronism, and mongolism, a hypothyroidism; (2) an adiposity occurring at the juvenile age indicates in eighty per cent of the cases insufficiency of the posterior lobe of the pituitary gland, usually associated with insufficiency of the anterior lobe; (3) an adiposity occurring in late adult life may be due to single or combined hypothyroidism hypopituitarism, or hypogonadism; and (4) an adiposity occurring in the juvenile or early adult life, however, could never be attributed to hypogonadism or hypothyroidism. In the same article we give other points for differentiating these adiposities, such as the distribution of the panniculus, associated endocrine signs, and the effects of therapy. There is, however, a great deal of contention regarding the etiology of adiposity. Professor Arthur Biedl, of Prague, is much inclined to attribute these obesities to a cerebral or hippocampal lesion. B. A. Houssay, of Buenos Aires, is more inclined to believe that he has proven experimentally that the lesion is located in the interpeduncular neighborhood of the pituitary gland, but not in the hypophysis itself. Aschner, of Switzerland, claims that lesions of the tuber cinereum have produced this classical type of adiposity in animals. Bremer, of Antwerp, and Bailey, of Boston, also are inclined to attribute these obesities, as well as other so-called hypophyseal signs, to extra-pituitary lesions of the hippocampal region. The French school, led by Camus and Roussy have maintained for many years that lesion of the hypophysis does not account for this type of adiposity nor for some of the other symptomatology attributed to the pituitary gland, and relate them to perihypophyseal lesions. Professor Julius Bauer, of Vienna, gives to the primary inherent gamete and zygote cells the property produced by chromosomal deficiency, the etiological factor in the production of adiposity. He claims that if the indi-

vidual cells producing this panniculus were dissected off one portion of the body, the hips, for instance, in the pituitary case, and engrafted upon the back of hand or the supraclavicular region, they would continue with the overgrowth and production of the adiposity.

Contrary to all this contention and, for the most part, physiological proof in animals, we have continued to believe that the majority of these juvenile obesities are due to internal secretory disturbance and that the adiposity in these particular cases is caused by deficiency of the posterior lobe of the pituitary gland. It cannot be disproved, however, that the function of this portion of the gland may not be influenced by lesions or nervous impulses coming from various portions of the brain, hippocampal gyrus interpeduncular region, tuber cinereum, etc. This boy (Case No. 1) does not show as decided an insufficiency of the hypophysis as the other two cases (Nos. 2 and 3), yet the adiposity is evident in ordinary street clothes and is very classical in its distribution. Besides the adiposity he has the characteristic small head, hands, and feet in comparison with the rest of the body. With the classical pituitary adiposity, limited to the girdle region, particularly the hip and shoulder girdles, the lateral aspects of the chest, and the lower portion of the abdomen, he has the mammary adiposity, which, occurring in the preadult age (in his case at thirteen) or in late adult life, indicates gonad insufficiency. For this reason we would suspect that he has a primary insufficiency of the *anterior lobe* pituitary gland, because we know that when the anterior lobe of the pituitary gland does not function sufficiently, it indicates that the gonads (testicles, in the male) will not develop properly. In these cases we would expect an absence of development of the generative organs during the age of adolescence. This, after all, is the most important circumstance to suspect and *prevent*, if possible, in these cases. It is well known that if in either sex there is an imperfect development of the generative organs at the adolescent age, there will be a very decided change in the psychic state, as well as in the future physical growth, of the individual. This maldevelopment will tend to prevent the proper contact and association of these individuals, with the consequent interference with their projection in social and business life. Whether or not we can predict the genital development of this case in the next



lief by treatment. In these conditions where we have a thyroid insufficiency added to a primary pituitary insufficiency we do *not* get an abnormal metabolic rate, which has misled a great many observers. Our experience in routinely examining about 2,500 endocrine disorders, 875 of which were pluriglandular, has led us to believe that the basal metabolic rate is not a guide to the function of the thyroid gland in pluriglandular disorders. This rate might be within the normal and yet the thyroid gland may be either very much increased or decreased in its function. While we have a great deal of confidence in the basal metabolic rate as a measure of thyroid function in simple uniglandular thyroid disorder, it is our opinion that the above statement maintains in all those conditions in which the thyroid disorder is only a part of a pluriglandular dyscrasia. We have proven this to our own satisfaction in obtaining remarkable therapeutic response to thyroid substitution in these pluriglandular disorders having a normal or even metabolic rate.

This introduces the subject of polypharmacy in the treatment of ductless gland disorders, i. e., *whether or not we should give a combination of various ductless gland substances in suspect pluriglandular insufficiency.* As a rule, we believe this method of pluriglandular therapy is very poor practice. It should not be attempted until one has had a great deal of experience in clinical endocrinology and has become quite expert in the exact diagnosis of pluriglandular disorders. We will progress more rapidly in both diagnosis and treatment if we give one ductless gland preparation at a time, and by watching the therapeutic reaction of this substance, determine whether, or not the patient has a deficiency of a single gland. In a given case which might be diagnosed, for instance, as thyro-pituitary (bilobar) deficiency, that is, insufficiency of the thyroid with both lobes of the pituitary gland, we would first substitute thyroid substance to tolerance, giving the desiccated gland, until the patient begins to have some signs of thyroid intoxication, and closely observe the effect upon the general symptomatology, such as the mental state, adiposity, changes of the skin and its appendages, and of other systems, as the cardiovasculorenal, etc. If the patient does not react to this satisfactorily, we would then withdraw the thyroid treatment and give pituitary treatment, using the substance from one lobe at a time, say the pos-

terior lobe. If this is not productive of the proper therapeutic response, we would then give anterior lobe substance, and if this is followed by no favorable reaction, a combination of the anterior and posterior lobe substances may be given, and possibly later the anterior and posterior lobe and thyroid preparations. The most convincing knowledge in both diagnosis and treatment of ductless gland diseases as has been said before, has been obtained in this way from observing the therapeutic response in suspect endocrines.

Case No. 3, a boy aged fourteen, has an obesity so striking that it is unnecessary again to call your attention to its girdle, mammary, and mons location. It is a sad implication on the medical profession that this outstanding sign, so easily recognized, is not taken for its face value as indicating probable pituitary deficiency. If recognized and treated in the early juvenile age the results are comparatively good with simple treatment; whereas, if it is neglected for a number of years, during which time there is a probability that the anterior lobe also has become underfunctionating, the reaction to treatment becomes less and less marked. We have realized that the *early diagnosis in these disorders* is very much more important than the early diagnosis in diseases of other systems, not only on account of the greater ease with which results are obtained from treatment, but, in addition, because the *disorder of other ductless glands* produced by the primary uniglandular disorder *is frequently prevented*. You will note in this case the same mammary adiposity present in the other two cases. On examining the testicles we find that they are about the size of a pea, and the penis is about the length of the terminal phalanx of the little finger. This hypoplasia of the genitalia, taken with the mammary adiposity at this age (fourteen) indicates that there is, in addition to the posterior lobe insufficiency, an insufficiency of the anterior lobe, and that it is probable that the genitalia will remain in an aplastic state as far as growth and development are concerned and consequently may have no function. Besides having a marked physical defect, such as the unusual adiposity and the underdevelopment of the genitalia, these individuals are social outcasts, having no generative function and consequently being denied the privileges of the marital and procreative states. The diagnosis made at the age of four-

teen in these cases, as stated before, is too late to produce the best therapeutic results. It should be made in the great majority of these cases many years before, when the adiposity begins to develop and the individual is overweight for his height and age. Treatment instituted at that time should prevent this enormous adiposity and the atrophy or tendency to hypoplasia of the generative organs.

Case No. 4 is a girl thirteen years old, weighing 230 pounds, who gives the following history: Her weight at birth was  $7\frac{1}{2}$  pounds, her teeth came in early, she walked before one year of age, and talked before the age of one, indicating that there was no possibility of her having had a congenital hypothyroidism. She has complained more or less of migraine and ocular symptoms during her childhood. Her mental development and progress through school have been normal. Her adiposity began about the tenth year and has increased very rapidly to the present age (weight now, at the age of thirteen, 230 pounds). She had one period 6 months ago, since which time she has had an amenorrhea. It is unnecessary to go into detail again regarding her adiposity, which conforms to the type demonstrated in the previous cases, but I wish to call your attention to the menstrual history, which is very characteristic in these cases, being analogous to the undergrowth and underfunction of the genitals demonstrated in the boy, Case No. 3. This girl had one period six months ago, since which she has had no periods or signs of menstrual activity. This is a very frequent occurrence in these cases, indicating the insufficiency of the anterior lobe of the pituitary gland, whose hormone is one of the regulating factors in the growth, development, and function of the genital system, as well as in the growth of the osseous system. Many of these cases do not have periods at all. We have now collected quite a series of women who have a primary anterior lobe pituitary insufficiency, of various ages, from fifteen to forty, with complete amenorrhea, the genital organs remaining infantile with regard to development, with complete absence of function. Besides longer or shorter periods of amenorrhea present in these cases, other aberrant forms of anterior lobe insufficiency have various types of menstrual imperfection, such as marked dysmenorrhea, metrorrhagia, and various combinations of these menstrual disorders. After all,

the hypoplasia of the genital organs is very much more important than the deformity caused by the adiposity subsequent to the insufficiency of the posterior lobe of this gland. The adiposity, at least, does not produce very marked changes, reflex or hormonal, in other systems; whereas an imperfect generative organ function disturbs the economy of the whole body, including the important functions of the cardiovascular, nervous, and gastro-intestinal systems.

Before dismissing this case as well as the others in this group, we wish to call your attention to the fact that in none of the simple pituitary deficiencies involving both lobes of the gland is there a defect of the mentality, so prominent in the cerebral adiposities and pure thyroid insufficiencies, some of which will be demonstrated in the next group. This mental state in itself serves to differentiate severe thyroidism from simple pituitarianism and also helps to determine whether or not the thyroid is involved with a pituitary insufficiency.

#### GROUP II, THYRO-PITUITARY (POSTERIOR LOBE) INSUFFICIENCY

This group consists of three cases of insufficiency of the thyroid gland which was present at birth (congenital hypothyroidism), to which was added later in the early juvenile life insufficiency of the *posterior lobe* of the pituitary gland. Before taking up these cases individually I wish to discuss the early signs of hypothyroidism, which should be known by every layman, as well as physician. These concern the signs presented from birth up to the first year of life, indicating normal or abnormal development, such as the weight at birth, the time of eruption of the first tooth, the time of walking and of talking. First, a normal baby would not weigh more than 8 pounds. An infant who does weigh more than 8 pounds at birth should be suspected of having a hypothyroidism. This would be the correct diagnosis in seventy per cent of the cases. With the exception of birth anomalies, such as hydrocephalus, monsters, etc., which can be excluded by inspection, the other thirty per cent of those overweight at birth usually turn out to be morons or mongols. A few babies who are overweight at birth do not develop later into abnormal children. Ninety per cent of the children giving histories of cretinism and positive hypothyroidism in later life, however, give histories of overweight at

birth, in addition to the other three cardinal signs. Second, the first teeth should be erupted not later than seven months, and all children who have been overweight at birth and do not have the first tooth at seven months should be suspected as probable hypothyroidisms. Third, a normal child should walk at the age of one year, and fourth, he should begin to put words together at the age of one year. If all these four cardinal signs are positive, further confirmation may be had with regard to the diagnosis of hypothyroidism by X-raying the hand, knee, and foot. At birth, the nuclei for the lower end of the femur and two tarsal bones (talus and calcaneus), should be present. At the end of one year there should be present two nuclei for the carpals (hamate and capitate), the distal epiphysis of the femur, the proximal epiphysis of the tibia, and those for three tarsal bones (talus, cuboid, and calcaneus). Dr. Alphonse McMahon and I have compared the development of the entire osseous system in the normal with the osseous development in various types of endocrines as shown X-rayically, in the *Journal of Endocrinology*, Vol. 8, No. 1, January, 1924. These studies are particularly valuable in the early diagnosis of hypothyroidism, the preadolescent diagnosis of anterior lobe pituitary gland insufficiency, and the diagnosis of hypogonadism in early adult life. When we realize the apparent poor results that have been obtained in the treatment of cretinism, we begin to appreciate the necessity of very early diagnosis, and by early diagnosis we mean in the first year of life, instead of at five or six years of age, the average duration of these cases today before treatment is instituted. The demand for thyroid hormone is so great during the first few years of life, when the entire nervous system, as well as the various other systems, normally is developing so rapidly that, unless the thyroid gland is properly functioning at this time, there is a retardation of growth and development in these systems which cannot be overcome, even if treatment is started in the juvenile age.

These three children belong to the same family. Case No. 5 is a boy six and one-half years of age, who weighed 8 pounds at birth. Case No. 6 is a girl four and one-half years of age, who weighed at birth  $8\frac{1}{2}$  pounds. Case No. 7, two and one-half years old, weighed at birth 8 pounds. The weight at birth of these three children should make the doctor suspicious at once.

He should at least inquire very carefully with regard to the future development of these children. Case No. 5 walked at ten months and talked at three years. Case No. 6 walked at fifteen months and started talking at four and one-half years. Case No. 7 walked at one year and is just beginning to talk (at two and one-half years). All, by the way, had poldactylism, Case No. 5 having had three extra fingers, Case No. 6 two extra fingers and one toe, and Case No. 7 one extra finger. We know the mental retardation in these children cannot be due to pituitarism, as has been stated in the discussion of pituitarism in the previous group. We also know that the adiposity in these children cannot be due to thyroidism, because we know that thyroidism does not produce an adiposity after the first one and one-half or two years. From the histories alone we can say that all three had more or less thyroid insufficiency at birth and during the first year of life. To this, however, has been added later in the lives of these children an insufficiency of the posterior lobe of the pituitary gland. This combination of thyro-pituitarism has been impressed upon us during our investigations in the last four or five years, and I believe it is one of the reasons for not obtaining better results in the treatment of these cases, for the majority of these children are treated as cretins and not as primary cretinism to which has been added a pituitarism. The pituitary insufficiency is given no consideration in the diagnosis or treatment. The diagnosis in these cases, on the contrary, has been considered so difficult that most physicians do not profess to be able to make it. Yet you see after all that the diagnosis is made upon such simple facts as the history of the first year of life and the advent of the adiposity, and it is just this gross objective sign and easily obtained information which we believe the most important diagnostic evidence in these cases.

#### GROUP III, THYRO-PITUITARY (ANTERIOR LOBE) INSUFFICIENCY

This is another group of thyro-pituitary insufficiency in which there was a congenital deficiency of the thyroid gland, to which later in life was added an insufficiency of the *anterior lobe* of the pituitary gland, without an involvement of the posterior lobe. Case No. 8 is a boy aged eleven, and Case No. 9 a girl aged nine, brother and sister. The girl is almost as tall

as the boy. Both have marked retardation in growth and some retardation in mentality. The early histories are as follows: The girl weighed  $8\frac{1}{4}$  pounds at birth, the first tooth appeared at the age of ten months, she walked at fourteen months, and did not talk until fifteen months. The boy weighed  $9\frac{1}{2}$  pounds at birth, his first tooth appeared at six months, he walked at fourteen months, and could not understand much that was said at two years. You will note that the chronological history in each case indicates the abnormal development which is so common in hypothyroidism, but instead of becoming obese later in life (as did Cases Nos. 5, 6 and 7), both these children have remained rather frail and undeveloped. In fact, it was this undernourishment and inability to gain weight which induced the parents to seek medical aid. Notice that neither has the adiposity that is present in the previous groups of pituitarism, either those complicated (Nos. 5, 6, and 7), or those uncomplicated (Nos. 1, 2, 3, and 4), by thyroidism. Besides this there is a very marked retardation in growth in these cases, that was not present in the thyro-pituitary individuals of the previous group (Nos. 5, 6, and 7), having the posterior lobe pituitary involved instead of the anterior lobe, as present in these two cases. We have noted for a considerable number of years that some cretins have remained unusually small and emaciated and free from adiposity, while others, who apparently were just as characteristic cretins from their first year history and mental retardation, have taken on an unusual amount of adiposity, and it was not until the last three or four years that we were able to explain the so-called emaciated cretin, as well as the obese cretin. When we compare this type with hypothyroidism in the adult we see that there is a similar type in the later ages. For instance, in the typical myxedema, which has been so well described by Sir Wm. Gull and Wm. Ord, we have a classical adiposity associated with the hypothyroidism; whereas in the "cachexia pachydermique" of Charcot or the "cachexia strumipriva" of Kocher we have a very marked cachexia following a complete removal of the thyroid. In the congenital thyro-pituitary (anterior lobe) deficiencies we have a very much more marked retardation of the osseous growth than in either simple thyroid or anterior lobe pituitary insufficiency.

The treatment in these cases of thyro-pituitary (anterior

lobe) deficiency, of course, is entirely different from that directed toward the simple thyroid or the thyro-pituitary (posterior lobe) insufficiency. In these cases an attempt should be made to substitute not only the thyroid deficiency, but also the deficiency of the anterior lobe pituitary gland; whereas in the thyroid and posterior lobe insufficiencies the treatment should be directed toward overcoming the decreased function of the thyroid gland, as well as that of the posterior lobe pituitary gland. It is very rarely noted that the cases have ever received more than simple thyroid substitution, and in most of these cases this treatment has not been instituted until after the thyroid, as well as the pituitary gland, had been functionless for a number of years, the body as a whole during this time having suffered the lack of both of these important hormones in its growth and development. In order to get the best results it is necessary not only to make the diagnosis in the first year of life, but also to give sufficient treatment at this time to overcome the thyroid deficiency, and this probably in itself would prevent the additional pituitary disorder which seems to be the logical sequence in untreated or insufficiently treated thyroid deficiencies. However, when the pituitary gland is already involved, the treatment must be directed toward its underfunction as well as the thyroid deficiency, taking into consideration the amount and duration of the disorder present, in order to accomplish as much as possible.

#### GROUP IV, THYROID INSUFFICIENCY

##### DEMONSTRATING IMPROVEMENT FOLLOWING EARLY DIAGNOSIS AND TREATMENT

Case No. 10 illustrates the effect of treatment in a case of thyroid insufficiency in which the diagnosis was made by Dr. E. P. Sloan of Bloomington, at the age of one year and treatment was given intensively at and subsequent to that time. This boy is now aged twelve. He weighed  $11\frac{3}{4}$  pounds at birth, his first tooth erupted at seventeen months, and he began to put words together at two years. Very early in the first year of life he began to have gastro-intestinal disturbances which were very pronounced. At the age of one year he first began to take thyroid treatment, after which the gastro-intestinal disturbances, such as nausea and vomiting, undernourishment, diar-



rhea, etc., improved very quickly and soon disappeared. This is another very important and common occurrence in hypothyroidism. The pediatricians have a great deal of trouble adapting a food to these children. They say they are very peculiar babies who do not accept the ordinary milk mixtures and for this reason are usually very much undernourished and have a great deal of trouble with their feeding during the first year of life. This boy (now twelve years of age) has been taking thyroid treatment ever since he was one year old. You will note that he is fairly well developed. He has some mental retardation, as shown by the history that he has some difficulty in school, but this is not marked enough to put him behind his classes. There is no question but that the early diagnosis and treatment has saved him from a complete mental as well as physical, deficiency. The question arises now whether he has not drifted into a partial insufficiency of some other ductless gland, in addition to his hypothyroidism. We would suspect that probably there is some anterior lobe deficiency in this case, in addition to the hypothyroidism. We feel sure that he has no posterior lobe involvement, on account of the absence of classical obesity which exists with deficiency of this lobe of the pituitary. In order to determine this it would be well to X-ray the bones for the ages of twelve (the elbow and carpals). In addition it would be well to X-ray the bones for the ages of eleven and thirteen. All these are given, with comparative tables and X-ray pictures for the normals and abnormals of the same ages, in the article on "Osseous Development in Endocrine Disorders" (Endocrinology, Vol. 8, No. 1, January, 1924). In the X-ray osseous studies of the endocrines we were very much surprised to find that the thyropituitary osseous development was advanced with regard to the appearance of the ossifying nuclei of the various bones for the age of the individual, whereas in the simple thyroidism, without a pituitary complication, there was a remarkable retardation in the appearance of the osseous nuclei as compared with the normal for the age. We feel that this is a very important diagnostic point, helping us to determine whether in a given suspect pluriglandular disorder having a definite thyroid involvement there is a complicating pituitary or gonadal element, which sometimes is

rather difficult of determination from the history and physical signs alone.

#### GROUP V, PLURIGLANDULAR INSUFFICIENCY, WITH EPILEPSY

Case No. 11 is a boy whose chief complaint is epilepsy. He has a very definite endocrine makeup, as will be seen from the various ductless gland signs, as follows: The orthodontial signs are marked in this case with very marked malocclusion of the teeth, some teeth being twisted almost half around in their sockets. The eyes show internal strabismus, which brings up another rather important point relating to the internal secretions. It is known that the eyeball accommodates itself to the bony socket containing it. The growth of the bones is under the influence to a large extent of the internal secretions. The anterior lobe pituitary, thyroid, thymus, and gonads particularly influence the growth and development of the various bones. When the bones do not grow properly the eye socket does not obtain its proper shape, consequently the eye is either too long or too short. This deviation from the normal in its axis prevents the rays of light from falling upon the retina in the normal way, and in order to overcome this error of refraction the ciliary muscles of the lens are put to a strain, and it is this strain which causes the infant to throw one eye past the normal meridian, producing strabismus or the so-called cross-eyed condition. This illustrates how the internal secretions dovetail themselves into almost every specialty, and no matter what fields of medicine we are practicing, we cannot afford to be without the information obtained in the study of this subject. The next meeting of the American Otolaryngological Association, to be held in St. Louis, is to devote the entire session to the study of the internal secretions as related to diseases of the nose and throat. This boy demonstrates the relationship of the internal secretions to the eyes and to the teeth, as well as to the mental makeup or nervous system, as shown by his epilepsy. Another important factor in his history is that these attacks of epilepsy stopped almost entirely during two months following the influenza, illustrating the effects of infections upon the functions of the ductless glands. We know that a great many disorders of the ductless glands follow simple infections, such as measles, whooping cough, diphtheria, influenza, typhoid fever, etc. Typhoid toxin particularly seems to

have a decided effect upon pituitary function. Influenza toxin probably has a more decided effect upon the adrenals, as exhibited by the prolonged malaise and extreme mental and physical fatigue following a severe attack of influenza. The general makeup and status of the osseous growth and the genital development in this patient go to speak for endocrine disorder. Examinations by two very good neurologists have failed to demonstrate any focal or local nervous lesion accountable for his epilepsy. The one ductless gland disorder with which epilepsy is most frequently associated is the pituitary, producing uncinate epilepsy, as it is now called. These epileptic attacks due to pituitary disease are usually preceded by disturbances of either the gustatory or the olfactory sense. That is, the patient during the aura or when recovering from the epileptic convulsion has a very marked perversion of the sense of smell or taste. If such a characteristic attack occurs having these peculiar gustatory or olfactory associations, that can be relieved by pituitary treatment, then we believe one is justified in saying that it is a case of pituitary epilepsy. We also have a peculiar attack of epilepsy in young children due to thymus disease, which is very easily relieved by X-ray of the thymus. We have had a number of cases of this kind having very severe epileptic convulsions, as frequently as two or three times a day for over a year, that we have relieved by one or two X-ray exposures of the thymus, completely and permanently for one and one-half to two years.

Epilepsy also occurs in a comparatively few cases of thyroid insufficiency, as has been proven by complete relief of the condition for a period of over five years by simple thyroid medication. As a whole, however, the percentage of endocrine epilepsy is small compared with the total number. We would say that not more than two per cent of the epilepsy have their etiology in the endocrinous glands.

#### GROUP VI, ANTERIOR LOBE PITUITARY HYPERSECRETION

Case No. 12, a boy twelve years of age, is one of hypersecretion of the anterior lobe of the pituitary gland. As has been stated, the anterior lobe pituitary gland has as one of its functions the stimulation of the osseous growth. It has been

termed by some the growth gland of juvenile life. We have known, for instance, children who apparently have stopped growing for a number of years to be stimulated in their growth by the administration of simple preparation of the anterior lobe pituitary gland by mouth and hypodermically. I know of one case of a child who grew five inches in the course of two years. Here is a boy twelve years of age who has an unquestionable overgrowth of the entire osseous system. There is a proportionate overgrowth of all the bones, showing that the condition producing it is more than likely an overfunction of the anterior lobe of the pituitary. You will note that his hand as compared with mine is about one-third larger, and he has a proportionate overgrowth of the short and flat bones, as well as of the long bones. One of his chief complaints is marked irritability and nervous instability. There are mental abnormalities which we have frequently noted with anterior lobe disorder, whether over- or undersecretion.

#### GROUP VII, RAYNAUD'S DISEASE

##### WITH DISCUSSION OF RECENT ENDOCRINE TREATMENT

Case No. 13 is a very interesting one of Raynaud's disease. This woman is thirty-three years of age and has had the condition of the fingers which you see, of very marked discoloration and atrophy of the terminal portions of the two middle fingers, symmetrically affected, resulting in amputation of the first phalanx of the middle finger of one hand, due to gangrene. The condition occurred a number of years ago, beginning with vasomotor changes. The fingers then became very blue, then purplish, and finally changed to a white pallor. Following this the terminal phalanx of one finger became gangrenous and had to be amputated. The symmetrical involvement of the fingers, taken with the history of early vasomotor spasm, followed by complete choking off of the blood supply at the ends of the fingers, resulting in gangrene, makes a very positive diagnosis of the rare condition known as Raynaud's disease. Besides this interesting vasomotor spasm of the fingers, she has a very typical adiposity, involving the girdle region, particularly the

inferior, and to a lesser extent the superior girdle. Associated with this she has had a very irregular menstrual life, the periods occurring at intervals of from three to five months and varying in amount and duration of flow. At times she has a metrorrhagia and at other times a very scanty, imperfect flow. This marked irregularity of the periods at the age of thirty-three, taken with the typical girdle adiposity, would make a very classical diagnosis of insufficiency of both lobes of the pituitary gland. She has been examined very carefully by Dr. J. F. Sloan of Peoria, who has noted a number of years ago a decreased metabolic rate and other signs indicating a secondary hypothyroidism, a complication of which we have spoken, in those cases of pituitary disorder which run a prolonged period of time. After the presence of this hypothyroidism for three or four years the function of her thyroid gland changed entirely so as to become oversecreting, and now she has a high basal metabolic rate. In spite of this high basal metabolic rate, however, she has been gaining in weight, which would indicate that she yet has a hypopituitarism with the hyperthyroidism. Dr. Sloan and Dr. Geo. Parker of Peoria have been giving her various ductless gland treatment in order to note any effect upon her Raynaud's disease. She has been obtaining a combination of ovarian and thyroid medication. She states that she is much better under this treatment.

The suggestion that I would make with regard to treatment is to try pituitary treatment in this case. There are now in the literature quite a number of cases of Raynaud's disease, in addition to other vasomotor disturbances, such as scleroderma and even minor dermal changes, as urticaria and erythema, which reacted very well to pituitary treatment. This treatment is given by exhibiting large doses of pituitary substance, posterior lobe, say 10 or 15 grains, in enteric capsules (coated with salol), by mouth, in addition to which is given Pituitrin (0) (Parke, Davis & Company) hypodermically, to the dose producing the intestinal reaction, consisting of abdominal cramps and defecation. The initial dose of Pituitrin (0) is 1 c.c. (15 minims), and this is increased 1 minim each day until intestinal cramps and defecation occur. This is considered the

maximum physiological dose and should not be exceeded for fear of producing the general reaction, consisting of emotionalism, tachycardia, syncope, etc. For a detailed account of pituitary treatment for any of the vasomotor skin diseases or pituitary insufficiency of the anterior or the posterior lobe, we would refer you to an article on "Endocrine Adiposity" in the Clinics of North America, St. Louis Number, Vol. 6, No. 1, 1922.

## SECONDARY OPERATIONS FOR GOITRE

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The matter of the secondary goitre operation is a very resourceful subject for thought and consideration by those of us who essay to "cure" goitres by surgical procedures. There is nothing more disappointing to the goitre patient than to have passed through an operation with the hope of relief, if not a cure, than to have to be subjected to it a second time, unless that be predicated as a probable necessity.

The conditions which primarily exist in pathological glands, and which may demand a second or even third operation, are practically three in number. The most offending of these three is found in the adenomatous type, where the gland is involved throughout by glandular proliferation, and from which a varying portion of the gland has been removed; and in which the process continues in the residue of gland left undisturbed. This form of *return of the goitre* is chiefly disappointing because of the resultant cosmetic defect after having undergone an operation. The second condition is found in the colloid goitre where a portion of the gland has been removed with anticipation of a recession in the part remaining, but where it persists in a deforming irregularity, with the further possibility of later developing toxicity. The third need of a further operation, after the primary one, may be found in any hyperplastic gland where an insufficient amount of gland tissue has been removed to effect relief of symptoms of toxemia.

We are convinced that all goitres begin as colloid goitres, which increase in size by hypertrophy because there is deposited within the acini an increased amount of colloid material. To accommodate this increase, the cells lining the acini become more columnar and their cellular nucleii perhaps enlarge. From such a goitre, if any symptoms or signs are present, they are due to pressure. We recognize this type as the adolescent goitre without toxic symptoms. This form may persist for a sufficiently long time to permit of a slight increase in the number of

the cells lining the acini; or, in some cases, an increase in the interstitial cells forming the framework of the gland, with or without the production of new acini. Where such acini are believed to have resulted from interstitial proliferation, there may be found within these walls new colloid substance.

All these proliferative forms are hyperplastic, and with any degree of hyperplasia, however small, we find some resultant hyperthyroidism, just as we believe that, without hyperplasia, we find no hyperthyroidism. The former type results in an adenomatous colloid goitre, while the latter is responsible largely for irregular types of former fruste.

Hyperplasia may assume different forms, as it grows from the acinal walls or interstitial tissue. One form of hyperplasia consists of a papillary epithelial proliferation of cells, which is found within the acini, taking up all their space so that there is practically no area remaining in the gland involved for storage or accumulation of colloid material. Such an hyperplasia is always associated with exophthalmic goitre and is supposed to be the only type of gland in which true exophthalmos is found.

Another form of hyperplasia which we will consider consists in proliferation of the acinal cells, either into the lumina of the acini, or between the walls of the acini and into the interstitial framework. Both these forms constitute the adenomatous type of goitre, and this type of hyperplasia usually has associated with it, sooner or later, certain forms of degeneration, and occasionally degeneration with secondary proliferation. *With the degeneration of any goitre there seems to be formed an altered secretion which is extremely toxic to the heart and nervous system, and this is specially true of the old adenomatous colloid goitres.*

In an operative experience of over 1,300 cases we have encountered the need of secondary surgical procedures in twenty-five cases. Two have been in the colloidal types, four in exophthalmic goitres, and nineteen in the adenomatous types. In eleven of the cases the initial operation was done by other operators and mostly in the largest goitre clinics in the United States. Fourteen were our own cases. The reason for making this differentiation is to indicate that in the inception of goitre surgery apparently all operators failed to recognize this possibility. Most of these cases resulted from the early efforts of the operators.



In the effort to reduce the time of operation only the main mass of an adenomatous goitre was attacked, and the remaining portion was not inspected. Then, too, there was ever present fear of removing too much of the thyroid tissue; particularly was this a factor in the colloid and adenomatous types. With the observations made, as time advanced, it became evident that the results were not always satisfactory. Some question arose as to whether the results in these cases justified the risks.

In the last few years it has been demonstrated that the subsequent operation is a safe and satisfactory step, only one fatality having occurred on the fourth post-operative day, supposedly from pulmonary embolism.

In considering the recurrence of the gland after operation, it may be safely said that this feature depends largely upon two factors: First, the amount and location of gland tissue diseased; second, the experience of the operator.

Discussing the first factor, we believe that, with a thoroughly degenerated adenomatous colloid goitre, the probability of recurrence will be present potentially in every case.

We believe that in the exophthalmic having one lobe more seriously affected than the other, a cure may be effected by lobectomy of the badly diseased lobe and resection of a part of the opposite lobe, usually found near the lower pole.

We further believe that a recurrent goitre may be operated on with comparative safety if the perverted secretion has not caused a thyrotoxicosis for too long a period. This may be true, likewise, in further recurrence for a third operation, of which we have had three successful cases.

In the adenomatous type, with more or less complete involvement of the thyroid, it was early evident that lobectomy was unsatisfactory because of the asymmetry resulting from thoroughly clearing one side of the neck, leaving a large mass of irregular thyroid tissue in the other; some effort was made to correct this by placing several deep sutures horizontally into the projecting portion of the gland nearest the median line, tying them tightly, and thus strangling such portions as were inclosed by the sutures. This procedure was of only slight benefit and did not prevent the further growth of adenomatous masses with degeneration, which occurred in the portion left undisturbed. It did, however, encourage the resection of certain isolated gland projec-

tions; and was the inspiration to what later became a complete resection of the remaining lobe.

This resection for recurrence is now definitely and satisfactorily accomplished in two different ways. If the gland is in lobulated formation from above downwards, as is frequently the case, then the most involved or degenerated portion of the gland is selected for complete removal. In the remaining lobules the most prominent one is selected for excision; and about it, in the contiguous thyroid tissue, a chain of deep sutures is thrown and tied, shutting off the blood supply in a measure from the portion to be removed; then the excision is made as the index finger lifts up on the posterior surface of the gland. As the deeper levels are reached the blood supply is not always under control from the preliminary suturing, and one must be prepared to add mattress sutures or others as need arises. When this step has been completed and all active bleeding has been brought under control, through and through sutures are placed in the sectional surfaces and the opening closed, thereby further overcoming any tendency to ooze, or a controlling suture to slip or cut out. In like manner more than one lobule can be removed.

A word of caution is here offered to the novice in thyroid surgery in attempting this performance lest uncomfortable bleeding ensue. Some knowledge must be had of the friability of the tissue; of how much pressure the tissue will bear from the sutures and where they should be placed. Such judgment only experience in goitre surgery will afford.

In the gland formation where no lobulation exists, but the mass is only an irregular structure made up of numerous small adenomatous foci, with little selection of the portion to be sacrificed, the resection should be a horizontal one of either an upper or a lower segment complete, according to which is the better tissue to leave. This section is fortified by a single cross chain of deep sutures and a ligation of the upper or lower pole leading to the segment taken away.

Utilizing again the value of experience, if the operator will make some little search he may discover a portion of normal thyroid tissue with an easy line of cleavage which makes this discard of the adenomatous portion comparatively easy. To be sure a portion of normal thyroid is often found thinned out

and distorted and one must be sure of his structure before making too great a sacrifice of tissue.

In a measure, having established the feasibility of resecting the thyroid gland under all operable conditions, the procedures are much the same as confront the plastic surgeon. Judgment must be directed during the operation to suit the formation and the character of the tissue, and as an essential adjunct to this fact the question necessarily follows: How much of the gland can be removed? It is our experience that this cannot be answered by measurements of portions. This again is a matter of judgment founded upon the history of the case and the character of the tissue as grossly revealed. This much has been established: that more can be safely taken away than has been commonly set down by rule. The more toxic a case is, or the more degenerate a gland is found to be, the greater should be the sacrifice of such tissue. As age advances there is manifestly less need of thyroid tissue; in fact, it is possible for a human being to live with practically no thyroid tissue, *if it be not all removed in one operation*, and an essential amount of glandular therapy furnished to the system afterwards. These facts are specially demonstrated in one outstanding case as reported herewith. Other observations have given us the same impression.

CASE: Miss P. K., dressmaker, age 62, single, white, American. Family history negative. Personal history, negative, except that in adolescence she developed a goiter which, while in evidence, remained quiescent until about the age of 50 years. At the age of 54 years a central mass of considerable size was removed (by another surgeon) and the lateral lobes evidently were not disturbed. After a few months it began to enlarge again slowly on both sides. Eight years later we performed a secondary operation for a large, degenerated bilateral adenomatous development. Without careful inspection of the entire gland prior to lobectomy the right mass was removed, presuming it to be the major portion. On examination of the left portion, however, a much larger growth was detected substernally, which was depressed deeply toward the spine, for which reason it was not at first glance in evidence. On delivery from the neck it was found so totally degenerated, with hemorrhagic areas and calcareous infiltration, that we dared not leave it in; and yet

we hesitated to remove the entire gland. As there was no alternative, practically all of the gland was taken, except small fragments left as substantial stumps for ligation at the poles. These were, of course, strangulated. The paratracheal areas containing what we hoped to be the parathyroid glands were carefully ligated so no injury would result to the parathyroids.

This patient was immediately put on a glandular therapy following operation. She left the hospital and about ten days afterwards discontinued medication.

She seemed to do well at home for several days and then became weak and had twitching of her muscles, particularly of the arms and legs. Her weakness grew rapidly and she became cachectic and emaciated and developed concurrently night sweats. In a few weeks she had become so weak and nervous that she could scarcely lift her head. In this condition we found her about three weeks after she had left the hospital.

She was slightly cyanotic, and had a rapid weak pulse, with a slightly subnormal temperature, nauseated and complained of a tightness in her chest which caused labored breathing and gave her a fear of impending death.

She was at once put on her medication and recovered slowly, under treatment, in about three months. Since then she has been perfectly well so long as she takes her thyroid and parathyroid capsules, but feels the return of the old symptoms when she leaves off.

She did not do well on thyroxin and had to be put back on thyroid medication.

Today, about one and a half years since her operation, she is better, she says, than she had been for twenty years prior to operation.

From the foregoing we wish to conclude with the following observations:

## CONCLUSIONS

1. That hyperthyroidism is the result of the secretion from hyperplastic goiters. That the amount of hyperplasia determines the amount of hyperthyroidism.

2. That the type of poison which causes the marked cardiac muscular degeneration and central nervous system deterioration, if not the entire organism, is dependent upon altered thyroid

secretions. That these altered secretions may be due to the degeneration of hyperplastic goiters with formation of leukomains, or again by some action on the other endocrines, the chief of which are the adrenals, causing lost or changed functions to them.

3. That the secondary operations may be definitely deferred by not waiting for involvement of the entire gland, there by recommending earlier but less radical operation.

4. That the rule of thumb cannot be used successfully in thyroid surgery as to how much gland shall be removed. This depends entirely upon the experience of the operator, as does the result of the operation.

5. That more thyroid tissue can be successfully removed at a secondary operation than is now generally supposed.

6. That secondary operations can be successfully performed. That these should be performed when, if not before, signs of thyrotoxicosis appear.

I have two very interesting cases furnished me by the local men that illustrate some phases of the subject.

This first patient, Mrs. J. P., is a woman, 38 years of age. Twelve years ago the left lobe, isthmus and anterior portion of the right lobe were removed at one of the largest goiter clinics in the country. Three years afterwards the right lobe was obviously increasing in size, and has slowly increased for nine years. As you see, it has crowded the trachea far to the left. One projection fills the supra-sternal notch, and there is probably an intra-thoracic projection on the right side. The pressure symptoms are marked, although not severe.

Four years ago she was thought to have tuberculosis in the right lung, but states that she never had much, if any, fever.

Her pulse rate is 120. The basal metabolism rate plus 10. She is remarkably free from tremor and eye symptoms.

One peculiarity of the case is that her systolic blood pressure is 145, while her diastolic is only 72.

This patient presents a typical picture of the kind of cases that I have been talking about.

This proliferation of the right lobe should have been removed several years ago when it began to cause trouble. She has fortunately gone nine years without becoming toxic. Undoubtedly some damage to the heart has occurred as evidenced

by the increased pulse pressure, and the sooner she gets rid of it, the better.\*

The second case is Mr. B. E. W. Six years ago he was suffering with an extremely severe exophthalmic goiter. A double ligation, performed at one of the largest clinics in the country, gave him no benefit. He returned to that clinic ten weeks afterwards and they advised against operation. Then he came to Bloomington and Dr. Sloan very properly removed most of the right lobe and a portion of the left. He recovered satisfactorily and was in comparatively good health for two years, then the remaining portion of the left lobe began to grow and his symptoms returned. He was subjected to X-ray and radium treatment for twelve months. At first he seemed to get some benefit, then gradually became worse. He made all arrangements to have a second operation and three days before he was to enter the hospital he sustained a cerebral hemorrhage. His right side was completely paralyzed for a time. Since that time his paralysis has been getting some better, but he is still markedly toxic.

This case is a spectacular example of the folly of delay. His only chance now is to have the rest of this left lobe removed.† This should be done as soon as his condition will permit. Had this left lobe been removed two years ago when his symptoms returned he would probably not have had this cerebral hemorrhage. In my opinion its removal at this time will improve his condition greatly.

\*"Mrs. J. P." was operated on one month afterward and a soft colloid mass as large as a grape fruit was removed from the right thoracic cavity with the right lobe. Her symptoms that indicated tuberculosis have all disappeared since the operation.

†"Mr. B. E. W." was operated on three days afterward and the left lobe removed. The remains of the left lobe had increased to about eight times the size it was at the time of previous operation. Hyperphlasia was present throughout. The improvement in the general condition of the patient following the operation is most decided.

## DIAGNOSTIC CLINIC

DR. W. WAYNE BABCOCK

PHILADELPHIA

9:00 A. M. Friday, January 25, 1924

CASE I: Toxic Adenoma in its Early Stage Exacerbated by Iodine.

This patient is a married woman twenty-nine years old who has had no children. The previous history shows a tendency to melancholia that has been marked during the last few years. For ten years the patient has noticed enlargement of the neck, which she believes has been more marked during the past year. For three months she has been taking two to five drops of tincture of iodine twice a day and finds that she feels no better, that her heart beats rapidly upon exertion, and that the neck has increased in size during the treatment. You will observe the symmetrical swelling of lower anterior part of neck made up of a moderately soft thyroid gland containing a palpable nodule in the left lobe near the isthmus about the size of a cherry. This patient weighed 109 pounds at marriage four and a half years ago and her present weight is 134. She has no tremor or headache, but has complained of palpitation and tachycardia the last six weeks. Apparently we have here a case of Plummer's Disease in the making. This is an adenomatous goiter with early toxic symptoms that have been aggravated by the use of iodine. Now is the time to protect the patient's heart from future degenerative changes, to prevent a future intense thyrotoxicosis. In this patient the prophylactic and curative treatment is both easy and safe. It consists in the enucleation of the adenoma. In this type of thyroid enlargement we know of no effective non-operative treatment.

CASE II: Toxic Adenoma advanced with Myocardial Degeneration.

Our first patient presented a toxic adenoma at the age of 29 years; our second patient shows the same condition 25 years later in life. The patient is a married woman, aged 53, who has had ten children and no miscarriages. She has noticed a thyroid enlargement for twelve years and for the past eight years has shown increasing nervousness and enfeeblement. An operation for pelvic laceration was done eight years ago and the patient thinks her heart has not been as good since that time. For six years she has been in the hospital off and on for severe cardiac disturbances. She was very ill last spring with a generalized edema and, as you see, is now very

weak, and shows marked tachycardia, marked cardiac irregularity and a marked tremor. There is a large bilateral thyroid enlargement, with enlargement of the isthmus and with multiple adenomas, producing a very nodular goiter you may easily recognize even at a distance. On palpation, after the method of Pottenger, of the chest we can make out what seems to be the left cardiac border well to the left of the nipple line, while the right border runs nearly two finger breadths to the right of the sternum. Pulsation of the veins of neck, with irregularity, and a thrill is shown. There is a moderate edema of the legs and the patient is hardly able to walk. The patient shows the advanced cardiopathy with decompensation from a toxic adenomatous goiter of twelve years duration. She illustrates what Doctor Jackson said yesterday, that it usually takes fourteen years or more for these adenomas to develop impressive toxic symptoms, while with the exophthalmic goiter they appear within a few months. Unfortunately, this patient did not accept or receive treatment while it was prophylactic and curative, and now the wreck is so complete that little remains to salvage. Advanced and hopelessly damaged as her heart condition is, let her enter a hospital, be digitalized and treated, with hope that it may even yet be possible to give some degree of relief by a thyroidectomy.

CASE III: Goiter with Hypothyroidism Secondary to Tuberculosis.

This patient comes to us with a moderate sized symmetrical enlargement of the anterior part of the neck. She is single and 32 years of age. For many years she had a contact association with a tuberculous stepmother. There has been expectoration, cough and weakness for the last six years, and she has been in a sanitarium for pulmonary tuberculosis for the last four years. Much of the time she has been able to work in the sanitarium as a bookkeeper. The patient's weight when she was admitted to the sanitarium was 92. At present it is 132. There is a persistent evening temperature of 99.4 degrees to 99.6 degrees F. There is no tremor, no tachycardia, and the patient shows no excitement or emotional stress on examination. The thyroid enlargement is quite uniform, rather soft and not vascular. The general expression of features is somewhat heavy and the skin rather pale, dry and thickened. This suggests a hypothyroid condition. An X-ray examination shows areas of fibrosis in both upper and lower pulmonary lobes and the apices. If you read the chest as Pottenger has suggested you will note on simple inspection the areas of subcutaneous atrophy that correspond quite accurately with the underlying pulmonary lesion shown on the X-ray plate. It strikes me that this woman is an example of thyroid enlargement and probably partial thyroid exhaustion, the result of constant demands made upon the gland by a chronic tuberculous toxemia. Infection tends to exhaust the thyroxin storage. There is great danger of overestimating the importance of the goiter and of



ascribing symptoms to a condition that is purely secondary to the pulmonary disease. With a patient of this type the metabolic test is of value, and we will expect a low reading. So often a patient who has had evidence of hyperthyroidism passes on into hypothyroidism, but continues to be treated as a case of thyrotoxicosis. My opinion, then, would be that here is a case of predominant tuberculosis of the lungs, with a secondary enlarged but exhausted thyroid gland. How unwise and how futile would an operation upon the thyroid gland be. Rather should we continue to treat the pulmonary condition and also try and give some relief to the depleted thyroid by iodine or thyroid feeding.

CASE IV: Four Years of Worry as to an Intrathoracic Goiter from an Unconfirmed X-ray Shadow.

This patient is an unmarried woman of 47 who entered a sanitarium for tuberculosis three years ago, and remained three months. When she entered the sanitarium she weighed 104 pounds, had morning expectoration, marked gastro-intestinal disturbances with vomiting, and the physical evidence of an early pulmonary tuberculosis. In the three months that she was in the sanitarium she gained eleven pounds. Since that time her weight has increased so that she now weighs 127 pounds, a gain of 23 pounds. She has a slight cough and slight expectoration. Some years ago she was told she was a bleeder because of hemorrhage following an operation on the nose. While in the sanitarium she had an X-ray examination which is said to have shown a marked enlargement of the thyroid gland, presumably an intrathoracic goiter. Inspecting the chest, we observe an intra-clavicular absorption of subcutaneous tissue, more marked on the right side than upon the left. There is no obvious goiter, no enlargement of the veins of the neck or chest, no evidence of tracheal compression or displacement, no evidence of pressure on the recurrent laryngeal, sympathetic or vagus nerves. This is a patient with the gastro-intestinal disturbances of pulmonary disease, who has no special nervous symptoms, no ocular symptoms, and, as you see, no cervical or thoracic symptoms. She has an arrested pulmonary tuberculosis and comes to us apprehensive from the fact that an X-ray examination indicated she had an enlarged thyroid, although she has no other evidence of thyroid disease that we have detected. This case suggests the danger of an unbalanced dependence upon a machine-made diagnosis. Contrary to the prevalent view, seeing is not necessarily believing with either the X-ray or the microscope. Both must constantly be checked and corrected by clinical observation. We should carefully question every diagnosis made in the laboratory that does not accord with the clinical findings. We should be instructed but never dominated by a laboratory report, and we should constantly realize the thousand and one errors in Roentgen interpretation. In a case like this I have opened the chest, at the insistence of a roentgenologist of international fame, and have found

nothing. It is unfortunate that this patient has been permitted to worry for four years by reason of an unconfirmed shadow on an X-ray plate.

Has this woman hemophilia, a disease usually transmitted by the female, who escapes, to the male, who manifests the delayed clotting time? While it is convenient to blame our post-operation hemorrhages upon hemophilia, we rarely can honestly do so. Surely, if this patient were a bleeder, she would have found it out years before the operation on her nose. Let us, however, determine the clotting time and carefully and judiciously review all of the evidence and, if possible, clear the patient's mind of the two worrying and apparently ill-founded obsessions as to intrathoracic goiter and hemophilia.

#### CASE VI: Neurasthenia with Goiter Phobia.

This patient presents numerous rather interesting symptoms referred to many parts of the body. She is 44 years old, married, and has had two children. Eight years ago she had an operation upon a nasal sinus, preceded fifteen years ago by a severe attack of tonsilitis. Since that time every winter, and nearly all winter, she has had trouble with soreness and choking of the throat. The tonsils are very small, and there is little evidence of disease in the pharynx. She has constantly sought treatment, but of late years the physicians have not introduced their instrument down low enough in the throat to satisfy her. She complains that every night she has constant dryness, soreness and choking in the throat. Her mother died of tuberculosis and the patient has an unproductive moderate cough. She speaks of severe pain and distress in the chest and indeed in every part of the body that is referred to.

This is the type of patient that we have always with us, a patient that suffers constantly and at the hands of many physicians, and really enjoys and devotes herself to miserable health. She has been treated for a great variety of conditions, and often with marked temporary relief, especially if some new or unusual type of treatment were used. If I should wish testimonials for some especially bizarre method of treating disease, I should like to have a series of patients of this type. They give a foundation of reported error for every new ism, cult and pathy, from Perkin's tractors to Abrams' oscilloclast. We are prone to think of these patients as being neurotic, as having symptoms that are functional or auto-suggestive, and as not having organic disease. They pass from physician to physician, as this patient has passed, now getting better, and now getting worse, and much of the time not being relieved at all. They are undernourished and poorly developed, and often show visceroptosis. Frequently, as in this patient, there is a history of tuberculous contact. If we carefully examine these patients we find that a large number of them have enlarged thoracic and mesenteric lymph nodes. They react to tuberculin injections, often violently. It has impressed

me that a very large percentage of these so-called neurotic patients are suffering from a chronic mild form of tuberculous toxemic, manifesting itself by symptoms that are referred to various parts of the body. I am reminded of the fact that the late Weir Mitchell, in his successful treatment of neurasthenia, was using the best treatment for tuberculosis at a time when we did not know how to treat tuberculosis as such. Rest and over-feeding, electricity, fresh air, and elimination of excitement are good things for patients with tuberculosis. I cannot but feel that many of these neurasthenic patients must be looked upon as suffering from mild inactive forms of tuberculosis. They must be protected from the profession, as they crave violent forms of treatment. Particularly do they easily acquire the progressive operation habit. A patient reveals the diagnosis when she has had the coccyx removed and the uterus or kidney suspended. It is a serious responsibility for a physician to start this operative habit. A woman who came to me some time ago had had twenty-eight operations and desired more. It is reprehensible to keep these patients continuously stirred up by local treatments of every accessible organ and to over-emphasize unimportant conditions in tonsils, sinuses, eyes, uterus or other organs. I may be wrong in this case, but it strikes me that the thing she most needs is a good old-fashioned family physician who will advise and protect her and keep her out of surgical clinics, and especially out of group clinics. The best results I have seen in this type have followed the use of tuberculin and an anti-tuberculous regime.

### GENERAL CONFERENCE BY DR. BABCOCK

The thyroid gland presents many intricate problems that have led to much diversity of opinion. With a pathology and physiology none too clear in the minds of those who have devoted years to the study of thyroid disease, it is evident that the subject must be a confused or perplexing one to those of us in the medical profession who have not specialized in this field. In an attempt to simplify and elucidate the subject, may not this society go on record? May it not serve as a guide to medical opinion in this field? I am curious to learn if our members do not substantially agree as to many matters relating to the thyroid, and shall therefore state a number of propositions for your discussion, acceptance or rejection. While time limitations will prevent us from touching but a few phases of the subject, I hope that at later meetings these "round table" discussions may be continued and elaborated. Because these propositions are put in affirmative form does not, of course, imply that they represent absolute truths.

1. Excluding inflammatory and neoplastic diseases of the thyroid, the various thyroid enlargements are expressions of different stages or variations in a single pathologic process. The thyroid gland may undergo hypertrophy, hyperplasia, a resting or colloid

stage, atrophy or degeneration. A single gland may pass through all these stages. The hyperplastic or hypertrophic gland is the simple struma, the parenchymatous goiter, or, if toxic symptoms are manifest, the exophthalmic goiter. If the hyperplastic tendency stimulates interstitial epithelial cell rests to growth, an adenomatous or nodular goiter results. Cystic, hemorrhagic, calcareous goiters merely express degeneration changes in the course of the single pathologic process. We should discourage classifications that give these conditions the status of disease entities. As this concept of goiter seems to have your general acceptance, let us take a second proposition.

2. Our concept of the thyroid gland is that it consists of three elements: First, a supporting connecting tissue; second, epithelial elements devoted to the secretion of thyroxin; third, colloid, which has a remarkable affinity for iodine and is devoted to iodine storage. Hyperplasia of the epithelial elements results from excessive functional demands and indicates hyperactivity or thyrotoxicosis. Excessive colloid usually indicates a gland at rest or with hypofunction. Normally, two per cent or more of the gland consists of iodine, if the iodine falls below one per cent, hypothyroidism may develop.

3. Hyperplasia of the thyroid or goiter follow increased physiologic demands, deficient iodine, infection, and removal of part of the gland. The greatest factor in endemic goiter is iodine starvation. As a corollary iodine feeding is the most important prophylactic measure against goiter.

4. The tendency for adenomas to develop in the hyperplastic thyroid is a racial one, absent in many animals, but occurring in the human and the rodent thyroid.

5. Adenomas of the thyroid are not amenable to treatment except by local destruction or eradication. By preventing thyroid hyperplasia we may prevent the formation of adenomas.

6. Infection, partial, excision, increased physiological demands, excite but do not produce goiter, if there is sufficient iodine supplied to the gland. If we supply patients with sufficient iodine during the periods of excessive thyroxin loss, such as puberty, pregnancy, lactation, during the menopause and times of great emotional stress and infection, so that the thyroid always has insufficient iodine in storage, we should prevent goiter. If this be true, should we not as a society spread and promulgate the ideas of iodine feeding. As a corollary is it not better to have only 5 per cent of goiters in a community with three per cent of adenomas excited to toxicity by iodine feeding, than to have 60, 80, 93 per cent of thyroid enlargements in the community and have only one or two per cent of toxic adenomas? Looking to the greatest good to the greatest number, we should be willing to accept the occasional danger from iodine feeding. With a toxic adenoma, the condition runs on for years with symptoms so slightly noticeable that severe cardiac damage usually occurs before the

patient seeks relief. Is it not better to excite these potential toxic adenomas at an early stage and so drive the patient to necessary treatment before the heart has been damaged, rather than to let the patient drift on into myocardial degeneration? The exophthalmic goiter gives a less serious involvement of the heart because the symptoms are more acute and develop within a few months. The toxic adenoma usually progresses 4, 6, 8, 10, 16 years before anything is done for the patient. It would be better if these adenomas were lighted into evident toxicity and enucleated early in the progress of the disease.

Let me turn over these propositions for your discussion.

DR. ARNOLD JACKSON: Theoretically what you say has a great deal in it, but I should hesitate to put it into practice for one reason. We know absolutely nothing of the etiology of exophthalmic goiter. What you say in regard to giving iodine during times of stress and during adolescence to prevent goiter I believe is advisable. Ten per cent of the adenomas develop in children, even in babies of two months, so that you would hesitate to advise giving iodine to children. In regard to giving iodine during pregnancy, I think it is a very good thing. At the time of menopause the same might be shown. It should be governed carefully, patients should be seen every two or three weeks and metabolic rate taken.

DR. ARN: I would be anxious to see how it would work out among the school children. We see 95 or 96 per cent of these children with adenomatous goiter. They should have general examination and not have iodine until they have this examination. You have given me an idea in regard to adenomatous goiters in young children. Four or five per cent will have adenomatous goiter. We hesitate to operate upon them at such an early age and so far have been turning them down. The thought comes to me would it not be wise to give these children iodine to see what effect iodine would have upon young thyroid cases. I do not believe it would excite toxic activity as in the adult, because back in the old days every case that presented itself to the family doctor was given a box of iodine ointment, regardless of whether the goiter was adenomatous or not. The adenomas that I have seen have been in people past thirty years of age. I have never seen adenomas in young children excited by iodine.

DR. ARNOLD JACKSON: Twenty-five per cent of the cases under twenty-five years of age are due to lack of iodine. I think iodine should be given to young children with adenoma in the hope of relieving stress on the gland, and carrying them over the age of puberty and then removing it.

DR. TIMANUS: I am glad to hear this discussion. It happens now that I am just starting this work and am anxious to know definitely about this. I am particularly interested to learn about the possibility of giving iodine to the mother. I think the only way to combat it would be pre-natal.

A few years ago I had a woman with a large adenomatous goiter. She told me that all three of her children were born with large thyroids but they later on receded.

DR. ARN: I think it is very important to give iodine to pregnant women and to rub iodine on the neck, as I stressed in my paper of yesterday.

DR. DRYER, AURORA: Is it not true that adenomas are of foetal origin? If this is the case, why don't they give iodine pre-natally?

DR. MOSCHELLE: Isn't it true that for many generations they have been giving blood remedies, especially in the spring, to purify the system? Many contained iodine, many contained arsenic. Especially were these given to the run-down girls of puberty age, blood out of order, aren't making grades in school, taking music lessons, caught in the stress of modern life, this class of girls were given "blood medicine." I am not in favor of giving the so-called "blood medicine," any more than I am in favor of giving iodine tablets promiscuously to children. If iodine in any form is given it should be given under the guidance of a physician who understands that child. If iodine is given to school children, it should be given under the supervision of the school physician, or someone working in conjunction with him. But is it not possible that the old-time doctor was right in his treatment of some of these types of cases?

DR. ARNOLD JACKSON: I want to compliment Dr. Babcock on his wonderful diagnostic clinic.

DR. BABCOCK: We realize that during the latter winter months and the early spring months there is the least iodine in the system, while the most iodine is found in the fall. This corresponds with the periods of greatest growth. School children grow four times as fast in the fall as in the spring. In answer to Dr. Dryer's question, I believe the term foetal adenoma refers to the histologic structure, which is without colloid filled acini, and does not indicate that the growth developed in the foetus. The proper development of the thyroid gland in the foetus seems to hinge largely upon sufficient thyroxin in the mother, and even an aplastic gland in the new-born may develop under iodine feeding.

DR. MOSCHELLE: This reminds us of the proprietary medicine manufactured by Burroughs & Wellcome Company of London. The sheep ate grass on the Scottish hillsides which was laden with spring rains, and they claimed that glands from these sheep were used in making thyroid extract.

DR. BABCOCK: Another phase of this interesting subject relates to the fragmentary evidence indicating a relation of the thyroid to diabetes. After the experimental removal of part of the pancreas and the production of pancreatic diabetes, the removal of the thyroid gland was followed by an improvement in the hyperglycemia and an increase in the number of the Islands of Langerhans in the remain-

ing portion of the pancreas. In a case of crisis following thyroidectomy in the Johns Hopkins clinic, the blood showed hypoglycemia and the intravenous injection of glucose was followed by the recovery of the patient. Should we consider thyroidectomy as a means of treating certain forms of diabetes?

# Editorial

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## DWARFISM, INFANTILISM, MIDGETS AND LILLIPUTIANS

The laity can be confidently expected to evince interest in bizarre types of human beings, and this morbid curiosity is demonstrated by faithful patronage of "side shows" and vaudeville where opportunity presents for gazing upon midgets, dwarfs and Lilliputians. Kings had their jesters and some of the famous ones can be identified as achondroplastic dwarfs. The medical profession has displayed a similar concern for these tiny people, consequent to which a voluminous literature has accumulated. Considerable confusion has resulted and the discriminating reader is sometimes perplexed by the bewildering multiplicity of terms; types of micromelia are recorded carelessly under the wrong title. Thus true infantilism may be classified as essential dwarfism; or a Paltauf dwarf, a Lorain type, a Brissaud type, or a case of Mongolism may be incorrectly designated as hypophyseal infantilism, thyrogenic or eunuchoidal.

Indeed, it is only fair to admit that no uniform classification has been agreed upon, nor can this be reasonably expected upon the basis of existing knowledge. Moreover, transitional forms occur not infrequently which present difficult differential problems, and make confusion worse confounded. That the incertory glands exercise a profound influence upon the development of some types of dwarfism and infantilism must be clearly recognized, but indiscriminate glandular therapy in all types is not commendable.

Complete maturity demands adult intelligence and psyche, adult stature with normal skeletal proportions, adult genitalia with normal secondary sex characters. Mental retardation in an adult, who has reached normal height and normal sex characters, should not be regarded as infantilism. A primordial dwarf with adult mind and genitalia is not an example of true infantilism. Nor should the term infantilism be applied to a eunuchoid of



normal height, possessing an adult mind. Childhood myxedema (a much better term, by the way, than sporadic cretinism) should not be confused with Mongolism, and neither are instances of true infantilism, even though skeletal undergrowth be a striking symptom in both. Frölich's hypophyseal dystrophy, even though it include skeletal undergrowth, and infantile genitalia is nevertheless to be sharply separated from true infantilism.

True infantilism is perhaps best defined as persistent juvenility, in which the skeleton and its proportions, the genitalia, and the psyche remain childish, the type first described by Lorain. Falta insists that this complex is not a primary ductless gland disease, but that the incretory organs are "childish" secondarily, merely in the same proportion as the remainder of the body. Others would consider this syndrome due to a pure anterior lobe pituitary deficiency. The controversy may be settled before long. "The proof of the pudding is in the eating," and the proof in this instance may be a therapeutic one. Diabetes responded promptly to insulin; and so will infantilism respond to a potent extract of the anterior hypophysis, if lack of this hormone be its cause. But the proof to be conclusive will necessitate not only increase in height, but also development of genitalia and the attainment of adult psyche. Meanwhile, until such a product is available, more extensive use of roentgenology in the differential diagnosis of dwarfism and infantilism is advisable, as recommended by Englebach and McMahon in their recent article on osseous development in endocrine disorders. The appearance of bone nuclei, and the closure of the epiphyseal lines can thus be determined, and this information in correlation with the rest of the clinical picture is important and helpful in recognizing the different types alluded to above.—H. L.

## Book Reviews

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TRAITE D'ENDOCRINOLOGIE. (Les sécrétions internes au point de vue morphologique, chimique, physiologique, pathologique et thérapeutique.) Prof. C. I. Parhon et M. Goldstein. Tome 1. LA GLANDE THYROÏDE. Paper, pp. 467, Jassy, "Viata Romîneasca," S. A., 1923.

This volume, the result of painstaking compilation, deals with the anatomy, physiology and physiological chemistry of the thyroid in its normal and abnormal relations. Though the phenomena incident to thyroid hypofunction are discussed satisfactorily and at considerable length, those associated with toxic goiter, especially the hyperplastic thyroid of Graves' disease, are not dealt with sufficiently to be of substantial value to the clinician. Here and there throughout the book casual reference is made to previous observations by the authors themselves, but the work contains little that is new, being essentially an annotated catalog of the observations of others. To those desiring an acquaintance with the literature on the thyroid, this book will serve as a useful guide.—I. B.

EINFÜHRUNG IN DIE KLINIK DER INNEREN SEKRETION. G. Peritz, Berl., 1923. S. Karger, pp. 257.

For many medical men books like Biedl's or Swale Vincent's are too long, and small "compendiums" like Weill's booklet too short. To them Peritz' book may be warmly recommended. It gives a critical review of facts that are really known in endocrinology. Pseudoendocrinology has been omitted and the reviewer, therefore, considers this book the best for the use of medical students. Most of the 31 illustrations are very instructive.—J. K.

L'OPOTHERAPIE EN CLINIQUE. A. Sartory, Scheffler & Moinson, Strasb., 1923. Imprimerie Gutenberg, pp. 206.

A book on organotherapy necessarily contains a great deal of nonsense, otherwise it would not treat the literature completely. This little book is one of the good sort. It contains a tremendous amount of nonsense as to the use of eye, skin, heart, etc., but the authors tell only what they have found in the litera-

ture and clearly show that they do not believe much of it. A most important feature of the book is its description of the way in which incretory preparations are manufactured and of how carefully such preparations need to be examined.—J. K.

LES GRANDES ENDOCRINES, LEUR VALEUR FONCTIONNELLE.  
J. Parisot & G. Richard, Par., 1923, G. Doin, pp. 248.

An excellent book containing nearly all of the functional tests recommended for the incretory organs. It is quite original and should be read by all clinicians. How often the bedside clinician would like to know whether the function of an endocrine gland is disturbed! This book nearly always answers such questions as satisfactorily as possible at the present time; the literature is reviewed in an almost complete and in a very critical way. The reviewer considers it, along with Biedl's and Vincent's monographs, as the best work available on endocrinology.—J. K.

INNERE SEKRETION UND ZAHNHEILKUNDE. II. Bacherer, 1923.  
Berlinische Verlagsanstalt, pp. 92.

The influence of the endocrine organs on the teeth is a rather poorly investigated branch of endocrinology. In this little book an attempt is made to bring together the literature on the subject. Although the author sometimes cites as facts things about which in reality our knowledge is defective (for instance, the pathogenesis of rickets; that the hypophysis is the seat of Fröhlich's disease), the book contains so many interesting and important features that no medical man will be sorry to have read it.—J. K.

# Abstract Department

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Behavior of Loewe's heart-strip preparations under different conditions. III. Adrenin action. [Das Verhalten des Herzstreifenpräparates (nach Loewe) unter verschiedenen Bedingungen. III. Weitere Versuche zur Kenntnis der Adrenalinwirkung.] Abderhalden (E.) & Gellhorn (E.), Arch. f. d. ges. Physiol. (Berl.), 1923, 199, 437-456.

Serum and plasma in amounts themselves completely inactive increase the action of adrenin on heart-strips by reduction of threshold and longer duration of action. This is not due to their colloid action, since very small amounts of amino-acids have the same action. The results suggest close dependence of the internal secretions on the diet. Serum and plasma hinder the oxidation of adrenin in Ringer's solution. Their ultra-filtrates have the same action in lesser degree. Amino-acids also possess this property, but carbohydrates only in concentrations which are not reached in the animal organism. Carbohydrates show this action in decreasing degree in the order maltose, lactose, galactose, sucrose, fructose, glucose. The thermostability of adrenin in Ringer's solution is increased by addition of amino-acids. The active group of adrenin is very resistant to hydrogen peroxide, temperature increase, and alkalies, changes in degree of action only appearing after some hours, and in stronger solution either not appearing or being delayed much longer. Hence the rapid disappearance of the rise in blood pressure after intravenous adrenin injection cannot be attributed to oxidative destruction of the adrenin.—A. T. C.

Carcinoma of the suprarenal associated with unusual endocrine manifestations. Keyser (L. D.) & Walters (W.), J. Am. M. Ass. (Chicago), 1924, 82, 87-88.

The case reported is of interest because enlargement of the thyroid, nervousness, tremor, tachycardia, hyperhydrosis, heat intolerance, dyspnea, choking sensations, precordial distress, increased appetite, increased metabolic rate, and hypertension were associated with suprarenal carcinoma. The dyscrasia of the skin and pilosebaceous systems manifested by erythema, acne, comedones and hypertrichosis, redness of the mucosa, and atrophy of the lingual papillae, weakness, fatigue, alopecia and suppression of menses, the change in voice, the increase in weight, all are suggestive of perverted function of the suprarenal cortex as determined from previous clinical evidence. The hyperglycemia and glycosuria

are difficult to account for. In a cursory review of the literature the authors did not find such an association of symptoms mentioned. The death following operation was of a type suggesting insufficiency of the suprarenal medulla, and the small suprarenal found on the right side more or less confirmed such a view.—Courtesy, J. A. M. A.

**Intracardiac injection of adrenalin.** Petit-Dutaillis (D.), J. de Chir. (Par.), 1923, 22, 503-630.

Petit-Dutaillis is prosecutor at Paris, and he is enthusiastic as to the value of local injection of 1 or 2 cc. of the 1:1,000 solution of epinephrin to revive the heart during collapse at operations. In 25 such cases published, permanent resuscitation was realized in 56%. The list of successful cases includes 3 of white syncope under chloroform; the interval in the successful cases was not more than 4 or 6 minutes. The nerve centers will not tolerate an anemia of more than 10 minutes at most. Especially instructive is Henschen's case in which a stab wound of the heart was being sutured and the heart action was stopping; the intracardiac injection revived the heart at once, and the operation was successfully concluded. He advocates introducing the long, fine needle in the fourth interspace, close to the margin of the fifth costal cartilage and close to the sternum, pointing the needle slightly toward the meridian line after the first 2-3 cm., thus injecting the fluid directly into the right ventricle. Necropsies and experiments on animals have demonstrated that the injury of the heart from the puncture is so slight as to be negligible. Artificial respiration and simple massage of the precordial region may be indispensable adjuvants. Some have given pituitary extract or strophanthin with the epinephrin, to prolong the action.—J. Am. M. Ass., 82, 502.

**Necessity for caution in the employment of high voltage roentgen rays as therapeutic agent against malignant disease: acute adrenal insufficiency and death sequelae.** Smithies (F.), Surg. Gynec. & Obst. (Chicago), 1923, 36, 61-63.

A case is reported of a man 58 years of age in whom death from Addison's syndrome occurred within 4 months after "deep" roentgen therapy of long duration and very high voltage. The roentgen treatment was for supposed malignancy of the spine which was subsequently shown to have been a faulty diagnosis.—G. E. B.

**Cholesterin formation in the animal body, (Über die Cholesterinbildung im Tierkörper).** Beumer (H.) & Lehman (F.), Ztschr. f. d. ges. exper. Med. (Berl.), 1923, 37, 274.

The authors discuss the two views concerning the origin of cholesterol in the organism: (1) (Chauffard's) that cholesterol is synthesized in the suprarenal cortex, and (2) (Aschoff's school) that the suprarenal merely acts as a storehouse for the cholesterol

from the food. Some of the important literature supporting and controverting these hypotheses is quoted. The possible relation of the spleen to the origin and deposition of cholesterol is mentioned. Beumer and Lehman took two litters of newborn pups weaned 4-7 days after birth. One of one litter and two of the other were killed for controls and their cholesterol contents determined. The remaining two pups (one of each litter) were fed on almost cholesterol-free diet of separated milk, maize, and cane sugar. They thrived fairly well on this diet. After 4 weeks the pups were killed and their cholesterol contents determined. The cholesterol balance was also determined by examination of the feces, the food intake having been accurately measured. Windaus-Fex method of estimating cholesterol was used. One of the pups showed an increase of 1.069 gms. and the other an increase of 1.561 gms. above their respective controls or twenty times the amount of cholesterol administered in the food. From this the authors conclude that the additional cholesterol was elaborated from substances in the food which are not extractable with ether.—S. Shapiro.

**Minor endocrine disturbances. Their metabolic and psychical effects.**  
Brown (W. L.), Brit. M. J. (Lond.), 1923, ii, 1073-1077.

Brown points out that it would be difficult to mention a drug which is clearly and beyond doubt of value in the treatment of disease and yet which possesses no known pharmacodynamic effects. Yet many of the extracts in common use have not been shown to have any such action. Even some of those which do cannot be used satisfactorily in substitution therapy. The early triumphs of thyroid medication tended to blind one to the difficulties surrounding the use of other glandular extracts in therapeutics. Yet the thyroid is exceptional in containing a definite reservoir of secretion and, by virtue of its duct originally opening into the alimentary canal, retaining the power of having its secretion absorbed by that route. It is perhaps fortunate that many of the preparations in use are inert, or otherwise damage might be done. Thus the injection of secretin by liberating an active pancreatic secretion may produce digestion of the intestine. It is just as well, therefore, that organo-therapy lags behind endocrinology.—J. Am. M. Ass., 82, 245.

**The role of endocrinology in epilepsy.** Kern (M.), Am. J. Clin. M. (Chicago), 1923, 30, 637-641.

Five cases of epilepsy were treated with a mixture of thyroid, pituitary and gonad extracts. In 4 the treatment was regarded as successful, in the other as a failure.—R. G. H.

**Osteomalacia in China.** Maxwell (J. P.), China M. J. (Shanghai), 1923, 37, 625-642.

The disease is common in certain parts of China, but is not attributed to an endocrine origin.—L. G. K.

**Familial muscular dystrophy—studies of six cases in one family.**

Mills (H. P.), Haines (T. H.) & Sessions (M. A.), Arch. Neurol. & Psychiat. (Chicago), 1924, **11**, 43-53.

Detailed metabolism studies were not possible in these cases, but the authors state that the findings obtained would not support the contentions of Janney and his collaborators in reference to the presence of hypoglycemia, as the fasting blood sugar in these cases was within recognized normal limits. The basal metabolism of these 6 subjects does not point clearly to either hyperfunction or hypofunction of the thyroid gland as the etiological factor of progressive muscular dystrophy. The findings in the 6 cases studied vary from minus 22% to plus 10%.—C. E. N.

**Racial and familial cyclic inheritance and other evidence from the mouse concerning the cause of oestrous phenomena.** Allen (E.), Am. J. Anat. (Phila.), 1923, **32**, 293-304.

Two variations in the usual cycle are described. Evidence is presented of racial differences and familial similarities in cycle length. Therefore, a genetic factor may be operating to partially determine cycle length. Reasons are given for believing that the presence of maturing ova in large follicles and their absence after ovulation or atresia is sufficient to explain the mechanism of oestrous phenomena. The author has isolated an active hormone from ovarian follicles which causes typical oestrous conditions in previously spayed animals, thus demonstrating the above conclusions. The continuation of ovogenesis during sexual maturity affords a distinct age difference in successive generations of ova and suggests a logical reason for their maturation at definite intervals.

—Condensed from Author's Abst.—W. J. A.

**Experimental transformation of sex in the domestic fowl by precocious ovariectomy (Transformation expérimentale du sexe par ovariectomie précoce chez le poule domestique).** Benoit (J.), Compt. rend. Acad. d. sc. (Par.) 1923, **177**, 1074-1077.

Two leghorn pullets, ovariectomized at 26 and (left side) at 4 days respectively, developed male characteristics in a few months. Exploratory laparotomy revealed an organ resembling a testis, and showing (in the first case) typical seminiferous tubules and even spermatozooids. After removal the secondary male characteristics disappeared.—A. T. C.

**Cyclic variation in uterine and tubal contraction waves.** Corner (G. W.), Am. J. Anat. (Phila.), 1923, **32**, 345-351.

There is, as part of the mechanisms of the oestrous cycle, a variation in the rhythm of spontaneous contraction of the uterine and tubal musculature. Small, rapid, undulatory contractions appear

in the tube of the pig just before the discharge of the graafian follicles, persist during the 3 days' time in which the ova are en route through the tubes, and disappear about the time the ova enter the uterus. The time of appearance of the undulatory contractions in the uterine musculature is synchronous with the period in which the ova, lying free in the uterus, either degenerate (if unfertilized) or begin the blastocyst stage of embryonic development. Upon the basis of these facts Corner has developed the hypothesis that the uterine and tubal contraction cycle represents a mechanism, probably peristaltic in nature, by which the ova are transported through the tubes and uterus.—Condensed from Author's Abst.—W. J. A.

**Sex development and behavior in female patients with dementia praecox.** Gibbs (C. E.), Arch. Neurol. & Psychiat. (Chicago), 1924, 11, 179-194.

A definite masculine type of pubic hair distribution occurred four times more frequently in the 310 psychotic patients than in the 235 nonpsychotic pregnant controls. Masculine type of pubic hair occurred in one out of every five patients with dementia praecox between the ages of 20 and 29, which was over five times more frequent than in normal controls and three times more frequent than in patients of other ages.—C. E. N.

**The oestrous cycle in the opossum.** Hartman (C. G.), Am. J. Anat. (Phila.), 1923, 32, 353-421.

The opossum is polyoestrous, having a single continuous breeding season from January to October, inclusive. Ovulation is spontaneous and occurs, on the average, every 28 days. Cyclic changes in oviduct, uteri, lateral vaginal canals (marsupial structures), vagina, and mammary glands are described and correlated with cyclic events in the follicular apparatus of the ovaries. In the living animal cyclic changes in the vaginal content were also followed; likewise the wave of growth and subsidence of the mammary glands. Fundamentally, these changes are similar to those in the Eutheria thus far studied and are due to the same stimuli; but the differences have proved instructive. Striking pseudopregnant phenomena of uteri and mammary glands are confirmed. Simple glands are found in the ampullae of the oviducts. They are probably responsible for the secretion of the shell membrane of the marsupial egg, hence homologous to similar glands of the Sauropsida.

—Condensed from Author's Abst., W. J. A.

**Ovarian insufficiency.** Hutton (J. H.), Illinois M. J. (Oak Park), 1924, 45, 37-41.

This is a good general review of the physiology of the ovaries in their normal and abnormal relations, the interrelationship of the ovaries with the other ductless glands, and the symptomatology and



treatment of ovarian insufficiency. Ovarian residue administered by mouth, subcutaneously or intravenously, is considered the best treatment.—I. B.

The mechanism of the sexual cycle, with special reference to the corpus luteum. Loeb (L.), *Am. J. Anat. (Phila.)*, 1923, 32, 305-343.

Loeb holds that the sexual cycle has periods which are successively under the control of the developing ovarian follicle and the corpus luteum. An analysis of the mechanism of the sexual cycle as a whole and a new classification of its periods are given; it is shown that the recent observations of Long and Evans in the rat and of Allen in the mouse are in agreement with the author's main conclusions, and that we must assume that in the rat and mouse the corpus luteum phase of the sexual cycle is rudimentary.

—Condensed from Author's Abst., W. J. A.

*Factors which cause cancer and the rapidity and frequency of cancer transformation* (Rapports quantitatifs entre les facteurs qui causent le cancer et la rapidité et la fréquence de la transformation cancéreuse). Loeb (L.), *Compt. rend. Soc. de biol. (Par.)*, 1923, 89, 307-308.

In the study of spontaneous mammary cancer in the mouse 2 factors emerge—heredity and ovarian internal secretion. Removal of the ovaries is an absolute preventive if carried out at a sufficiently early age. Once ovarian function is established, removal of the ovaries diminishes the frequency of occurrence in proportion to its early performance, but this procedure has no effect once the neoplasm has started.—*Physiol. Abst.*, 8, 423.

The behavior of the germinal epithelium in testis grafts and in experimental cryptorchid testes (rat and guinea pig). Moore (C. R.), *Science (N. Y.)*, 1924, 59, 41-44.

Testis and ovarian grafts made subcutaneously, intramuscularly, and intraperitoneally into normal females and normal males on recovery showed active cell division in the tubules. No spermatozoa were found. If the testicle is held in the peritoneal cavity the germinal epithelium degenerates and the interstitial tissue is increased. Grafts of testis made into the scrotum later showed some normal tubules possessing spermatozoa. The increased temperature is held to be an important factor in producing degeneration in the germinal epithelium when grafts are made elsewhere than the scrotum.—G. E. B.

Oestrous in mammals from a comparative point of view. Papanicolaou (G. N.), *Am. J. Anat. (Phila.)*, 1923, 32, 285-292.

The author calls attention to the varieties of oestrous in dif-

ferent mammals and to the fragmentary and incomplete condition of our present knowledge of the oestrous problem.

—Condensed from Author's Abst., W. J. A.

The influence of the uterus and the ovary on development of the mammary gland (*Über den Einfluss des Uterus und der Ovarien auf die Entwicklung der Brustdrüse*). Plaut (R.), *Ztschr. f. Biol.* (München), 1923, 79, 263-276.

• Injections of lipid extracts of placenta produce with young animals (guinea pigs, rabbits, cats) of both sexes, at first growth and secretion of colostrum, afterwards arrest of development, and finally degeneration; no formation of gland tissue. The extract has no effect upon adult males. The lipid extract of the ovary produces a growth of the uterus and appendages in young animals, and is without effect upon the mammary gland only if the uterus is present.—*Physiol. Abst.*, 8, 532.

X-ray stimulation of the ovary (*Reizbestrahlung der Ovarien*). Schönhof (C.), *Wien. klin. Wchnschr.*, 1923, 36, 877.

A girl of 22 began to gain weight; menstruation gradually ceased; abnormal hair growth appeared and there was hypoplasia of the generative organs. X-ray treatment caused loss of the abnormal hair and return of normal menstruation. Similar results were secured in a second case of amenorrhea.—J. K.

The general morphological and physiological significance of the oestrous problem. Stockard (C. R.), *Am. J. Anat.* (Phila.), 1923, 32, 277-283.

The usefulness of the vaginal smear method in determining the exact stage of the oestrous cycle is pointed out. The problem thus becomes, in the author's striking phraseology, "not an ordinary histological or morphological one, but a problem in living morphology." The cycle of morphological changes, which may be very readily recognized, gives an indicator for the occurrence of most complex physiological reactions which thus lend themselves to the morphological method of analysis.

—Condensed from Author's Abst., W. J. A.

The adult equivalent of the Froelich syndrome. Abbott (G. P.), *Calif. State J. M.* (San Fran.), 1924, 22, 20-21.

There is a type of hypopituitarism in adults, of subacute onset, which in many respects resembles the juvenile Froelich syndrome. Its etiology is traceable to infections, especially influenza and measles. The condition is characterized by adiposity, scanty menstruation or amenorrhea, lassitude and headache. Though the adiposity and amenorrhea are not influenced by pituitary or ovarian

opotherapy, the headache and lassitude are relieved by feeding whole pituitary.—I. B.

**Further investigation on the oxytocic-pressor-diuretic principle of the infundibular portion of the pituitary gland.** Abel (J. J.), Rouiller (C. A.) & Geiling (E. M. K.), *J. Pharmacol. & Exper. Therap.* (Balt.), 1923, **22**, 289-316.

The oxytocic substance of the infundibulum was isolated in such a degree of purity as to be from 1000 to 1250 times more active for the virgin guinea pig's uterus than the equivalent amount of the acid phosphate of histamine. The product, a tartrate, caused pronounced contractions of the virgin guinea pig's uterus in a dilution of 1:18,750,000,000. This product possesses pressure, diuretic, and respiratory properties. All these properties are believed referable to one and the same substances.—G. E. B.

**A preliminary therapeutic study of the active principle of the infundibular portion of the pituitary gland in four cases of diabetes insipidus.** Abel (J. J.) & Geiling (E. M. K.), *J. Pharmacol. & Exper. Therap.* (Balt.), 1923, **22**, 317-328.

The substance referred to in another paper as the oxytocic-pressor-diuretic principle of the infundibulum when used therapeutically showed distinct antidiuretic properties.—G. E. B.

**The mechanism of diabetes insipidus (Sur le mécanisme du diabète insipide).** Camus (J.), Gournay (J. J.) & Fiterre, *Compt. rend. Acad. d. Sc. (Par.)*, 1923, **177**, 289-291.

Polyuria following lesions in the opto-peduncular region in the base of the brain is accompanied by marked lowering or total disappearance of uric acid from the urine. If the onset of polyuria is delayed the uric acid may disappear earlier. Purine bases and phosphates are increased. These phenomena occur in dogs with experimental polyuria lasting only some days, and also with permanent polyuria (over 4 years). Since caffeine and theobromine are diuretics, it is suggested that the diuresis is connected with degradation of nucleoproteins and excess formation or non-transformation of diuretic purine bases.—A. T. C.

**Pituitrin in the treatment of asphyxia pallida neonatorum.** Cormack (J. G.), *China M. J.* (Shanghai), 1924, **38**, 42-43.

Two refractory cases of extreme asphyxia of new-born Chinese infants are reported in which prompt initiation of breathing followed intramuscular injections of 0.3 cc. of pituitrin.—R. G. H.

**Degeneratio adiposogenitalis.** Hirsch (O.), *Wien. klin. Wchnschr.*, 1923, **36**, 822-823.

In a man of 36 with tumor of the hypophysis and symptoms of

Fröhlich's disease x-ray therapy had no influence. The patient became almost blind. Operation was performed and 4 months later in both eyes visual acuity was 6/8 and the visual fields were nearly normal. The tumor was an adenoma. A woman of 46 was observed with cyst of the hypophysis. One eye was blind; the other showed 1/20 acuity. After operation the second eye became normal. Twice recurrence of the tumor made an operation necessary.—J. K.

**Acromegalic gigantism with dystrophia adiposogenitalis (Gigantisme acromegalique avec syndrome adipo-so-genital).** Schaeffer (H.) & Denoyelle, *Rev. neurol. (Par.)*, 1923, 30, 346-350.

Report of a case of infantile gigantism, subsequently acromegaly, with the syndrome of dystrophia adiposogenitalis fruste. This case is discussed in reference to the work of Camus and Roussy and Bailey and Bremmer in discriminating between the manifestations of a disturbance of the hypophyseal function and that of a center in the infundibulum. The occasional association of acromegaly and dystrophia adiposogenitalis does not seriously militate against the nervous origin of the latter, as it is possible that this condition is the result of compression of the neuro-vegetative center by the progressive development of a hypophyseal neoplasm.—C. E. N.

**The production of the adiposogenital syndrome in the rat, with preliminary notes upon the effects of a replacement therapy.** Smith (P. E.), Walker (A. T.) & Graeser (J. B.), *Proc. Soc. Exper. Biol. & Med. (N. Y.)*, 1924, 21, 204-206.

The authors have a method of injuring the hypophysis without damaging the brain. After this operation one rat showed a cessation of the oestrous cycle and reduction in size of the ovaries and uterus. Injections of anterior lobe substance restored ovulation. This experiment is cited as strong evidence of the hypophyseal etiology of the Fröhlich syndrome.—J. C. D.

**The seat of action of insulin (Über den Angriffspunkt des Insulins).** Ahlgren (G.), *Skandin. Arch. f. Physiol. (Berl. & Leipz.)*, 1923, 44, 167-185.

Fresh tissue substance from normal and from totally depancreatized animals was used. Capacity for decolorizing methylene blue was utilized as a measure of respiration. Tissue which did not utilize glucose spontaneously did so after the addition of suitable amounts of insulin. Fructose and galactose were utilized without insulin. Insulin did not hasten the oxidation of beta-oxybutyric acid and lactic acid.—G. E. B.

**Normal standards in treatment of 100 cases of diabetes with insulin.** Barach (J. H.), *J. Am. M. Ass. (Chicago)*, 1924, 82, 347-351.

Barach emphasizes the fact that in determining the diet of the diabetic patient three primary needs must be met: (1) caloric requirement; (2) maintenance of protein requirements of the body; (3) if the carbohydrate, protein and fat are given in wrong proportions, certain diseased states of the metabolism—ketosis—will follow with deadly effects. Present-day authorities on metabolism are generally agreed that 1 gm. of protein per kilogram of body weight is a safe protein ration. The largest amount of carbohydrate is given that the patient can tolerate without glycosuria and hyperglycemia. Sufficient fat must be given to meet the caloric requirement of the patient, avoiding large amounts which predispose to ketosis. The total glucose in these diets is estimated by adding the carbohydrate plus 58% of the protein plus 10% of the fat. Ladd and Palmer have adopted the simple ratio of 4 gm. of fat for each gram of carbohydrate in the diet. That 58% of the protein is directly available as carbohydrate has not yet been proved to the satisfaction of all workers in metabolism. Every-day experience with diabetic patients has shown Barach that the nervous make-up of diabetic patients of the same age, height and weight is an important factor in determining the food requirements for active life. The various formulas now in use do not and cannot include this variable factor, and therefore are not so applicable as they may seem. Barach believes, with Allen, that the arbitrary rule of estimating the metabolic needs of the diabetic patient by theoretical calculations is inaccurate, but he does not lend himself, as Allen does, to guess at the diet. In the absence of a better method and one which is beyond criticism, Barach follows the normal diet as near as the patient's diabetic state will permit. So-called normal diets, based on municipal statistics, are on the basis of carbohydrate, 67%; protein, 16%, and fats, 17% of the total. For the needs of the hospitalized ambulatory patient 30 calories per kilogram of body weight is allowed. The diabetic patient cannot assimilate the normal amount of carbohydrate. Experience in 100 hospital cases this year has shown that only one patient could take more than half the normal amount of carbohydrate. The diabetic patient does not do well on excessive protein. A normal diet offers about 1.25 gm. of protein per kilogram. Allowing a nearly normal amount of protein, 1 gm. per kilogram and as much carbohydrate as the patient can take, the remaining caloric requirements are furnished in fat. Being guided by the glucose output in the 24-hour specimen of urine, averaging this output every 2 or 3 days, the carbohydrate intake is reduced from time to time as needed. At each reduction of carbohydrate, fat of equal caloric value is added. Ordinarily the patient is made sugar free in 6 to 10 days. If by this process of exchange the patient cannot be rendered sugar free or attain nearly a normal blood sugar on a satisfactory maintenance diet without the presence of acetone or diacetic acid in the

urine, insulin is added in the treatment, enough being given to allow the patient a carbohydrate and fat intake for a good maintenance. At the time of leaving the hospital, the patient is usually taking 35 calories per kilogram, having gradually worked up to this point. A detailed survey of the first 35 patients showed that at the end of the year 13 were taking more food, and in 20 it was thought best to continue the same diet. In one case it was found necessary to lower the total food intake. In these 35 patients 27 are taking the same dosage of insulin. Seven are taking less insulin than they did when leaving the hospital, and in 5 it was necessary to increase the amount of insulin to maintain the total food tolerance and the desired nutritional state. In the 5 taking more insulin, intercurrent acute infections seemed to precede, if they were not the main cause, of the lowered tolerance. In these 35 cases there was a weight increase in 25 ranging from 3 to 30 pounds (1.4 to 13.6 kg.). In 8 there was no increase, and in 2 there was a loss of weight. Six patients gained 2 to 6 pounds (1 to 2.7 kg.). Nine patients gained from 5 to 10 pounds (2.3 to 4.5 kg.). Five patients gained from 10 to 20 pounds (4.5 to 9 kg.). Five patients gained from 20 to 30 pounds (9 to 13.6 kg.). Of these 35 patients, the outlook is good in 26. These are practically without conditions. In 9 cases the outlook is fair. Of those in whom the outlook today is only fair, it is evident that better conditions in the home and economic betterment would tend to place them in the more favorable class.—Courtesy A. M. A.

**The effect of the oral administration of alcohol upon the blood sugar of rabbits.** Blatherwick (N. R.), Maxwell (L. C.) & Long (M. L.), *Am. J. Physiol.* (Balt.), 1924, **67**, 346-347.

When insulin dissolved in dilute alcohol is given by stomach the blood sugar is decreased as much as 30%. Further investigation led the authors to believe, however, that the alcohol alone is responsible for this decrease and that there is no absorption of insulin.—T. C. B.

**Treatment of diabetes with insulin.** Blum (L.), Carlier & Schwab, *Bull. Soc. méd. d. hôp. (Par.)*, 1923, **47**, 1789-1797.

The authors relate several clinical histories showing the dangers of suspension of insulin treatment in severe cases of diabetes. In a man of 35 the fatal intoxication began 48 hours after the last injection, and death occurred 5 days later. He had been treated with insulin at the hospital and continued the injections on returning home until his supply failed and he had to stop. Increasing weakness set in and was followed by coma. In their second case, the number of injections was reduced after the patient had asked that they be interrupted. Glycosuria and acetonuria reappeared and increased rapidly. Forty-eight hours later the patient

was in coma. Very large doses of insulin were injected immediately, and 24 hours later the intoxication disappeared. Similar disturbances during treatment are due to complications which lower the carbohydrate tolerance, making thus the doses insufficient. They believe that the danger of discontinuing the injections lies in the lack of preparedness of the organism for the acid intoxication. The danger is less in children than in adults, because the islands may have regenerated in children. Diabetics should always keep a reserve supply of insulin to continue the treatment, and to cope with unforeseen complications susceptible of aggravating the diabetes. If they have to discontinue the injections, they should fast and use large amounts of alkali. Only when the urine is alkaline can immediate danger be considered averted.

—J. Am. M. Ass., 82, 423.

Some effects of insulin and glucokinase on maize seedlings. Ellis (M. M.) & Eyster (W. H.), *Science* (N. Y.), 1923, 58, 541-542.

In solutions of 1.0% to 0.005% growth was retarded in proportion to the amount. In weak solutions (less than 0.005%) some beneficial effects were shown.—G. E. B.

Basal metabolism in diabetes (Ueber der Grundumsatz bei Diabetes mellitus). Feyertag (H.), *Wien. klin. Wchnschr.*, 1923, 36, 823.

Falta, disagreeing with Benedict, Joslin and others, has always stated that even in the most serious cases of diabetes the basal metabolism is not increased. The author examined 3 serious cases of diabetes and studied the basal metabolism with and without insulin treatment. No difference was seen after injection of insulin. This is an argument in favor of Falta's theory.—J. K.

The insulin treatment of preoperative and postoperative nondiabetic acidosis. Fisher (D.) & Snell (M. W.), *J. Am. M. Ass.* (Chicago), 1924, 82, 699-700.

Two cases of preoperative acidosis due to starvation and incessant vomiting induced by an acute abdominal condition are reported. The action of insulin and glucose was specific. A third case of postoperative acidosis of a rather severe degree was practically unchanged at the end of twenty-four hours by the use of glucose alone by rectum. The subsequent administration of insulin brought about an immediate disappearance of the ketosis.

—Courtesy A. M. A.

Attempts to maintain the life of totally pancreatectomized dogs indefinitely by insulin. Fisher (N. F.), *Am. J. Physiol.* (Balt.), 1924, 67, 634-643.

Some pancreatectomized dogs can be kept alive for at least 8 months. The normal body weight is not maintained, and there

is polyphagia and polyuria, even when no sugar is present in the urine. Others die in spite of insulin control of hyperglycemia. The determining factor for survival seems to be a regeneration of pancreatic tissue from the duodenal stump of the duct.—T. C. B.

**Insulin as an investment for the patient with diabetes mellitus.**

Fitz (R.) & Murphy (W. P.), J. Am. M. Ass. (Chicago), 1924, 82, 435-438.

There are two classes of diabetic patients: those to whom insulin is a necessity and those to whom insulin is a luxury. Fortunately, diabetes is inherently a mild disease, tending to occur in people past the middle period of life and often lasting for years without producing any notable disability. Therefore, the group of patients to whom insulin is a necessity is comparatively small and does not represent more than a third of any large series. As a general rule, insulin should be given in all cases of diabetes occurring in children and in people under 40; in all cases of coma or severe acidosis; in all cases complicated by an infectious process which has caused either a temporary or a permanent lowering of tolerance; in all cases of proved severity in which there is necessity for a surgical operation, and in all cases in which the tolerance without insulin, as determined by adequate dietetic control, is so low as to make efficient living impossible. No one should hesitate to urge such patients to take insulin at all costs, for the drug may be life-saving and almost always represents a sound financial investment for the patient, with a big dividend of strength and vitality. Insulin, on the other hand, is a luxury for patients with mild diabetes who are seen most commonly. Almost all of these patients, if the disease is uncomplicated, have a high tolerance and do well for years on a reasonably restricted diet. Insulin offers them but little as a financial investment. If patients of this type wish to take small doses of insulin and can afford it, there may be no reason why they should not, and for a few cents' worth of insulin a day add a certain amount of extra food to their diets. They should not, however, be advised to take the new drug; rather should they be encouraged to get along without it as far as possible, or to use it sparingly. The discovery of insulin marks a wonderful advance in the treatment of diabetes, but it must not be abused. The best economic use of insulin will be made by the conservative practitioner, who saves money for the majority of his diabetic patients by keeping them sugar-free and in good condition without the trouble and expense of the drug, but who holds it in reserve for his severer cases for use in as large amounts as are necessary to produce definite results.—Authors' Conclusions.

**Physiological action of insulin** (*Sur l'action physiologique de l'insuline*). Gonzalez (P.) & Carrasco Formiguera (R.), *Compt. rend. Soc. de biol. (Par.)*, 1923, 89, 1237.



In general, from the point of view of the onset of convulsions, the less the weight of the rabbits, the more sensitive they are to insulin.—T. C. B.

**Basal metabolism in experimental diabetes** (*La dépense de fond dans le diabète pancréatique expérimental d'après les échanges gazeux. Action de l'insuline sur cette dépense*). Hédon (L.), *Compt. rend. Acad. d. sc. (Par.)*, 1924, **178**, 146-148.

The basal metabolism is increased in dogs after total pancreas removal by from 30 to 40%. This cannot be entirely due to disturbance in carbohydrate metabolism, since dogs in which at complete pancreatectomy a small portion was transplanted under the skin of the abdomen and which showed no glycosuria showed a marked increase in basal metabolism, which was not further increased after removal of the transplant and onset of glycosuria. The total gaseous exchange is markedly increased after total pancreas removal, and injection of insulin sufficient to cause the disappearance of glycosuria and lowering of blood sugar to normal, although it increases the respiratory quotient, does not restore the total gaseous exchange to normal. The increase after total pancreatectomy probably is due to increased protein and fat catabolism, independent, to a certain degree, of the carbohydrate disturbance.—A. T. C.

**The presence of an insulin-like substance in gastric and duodenal mucosa and its relation to gastric secretion.** Ivy (A. C.) & Fisher (N. F.), *Am. J. Physiol. (Balt.)*, 1924, **67**, 445-450.

An insulin-like sugar reducing substance is present in hog's gastric and duodenal mucosa, but is much less than in cattle's pancreas.—T. C. B.

**Treatment of diabetes** (*Zur Therapie der Diabetes*). Jaksch Warthenhorst (E.), *Wien. klin. Wchnschr.*, 1923, **36**, 844.

The author found that administration of some ethereal oils or allyl compounds prevents the unfavorable effects of insulin. Some cases of glycosuria are not benefited even by large quantities of insulin.—J. K.

**he routine treatment of diabetes with insulin.** Joslin (E. P.), *Tr. Ass. Am. Physicians (Phila.)*, 1923, **38**, 374-381.

If insulin is to serve its purpose, it must be emphasized that successful treatment of diabetes mellitus depends upon the utilization of all approved measures without insulin. Adherence to the proper diet, avoidance of extreme undernutrition or overnutrition, and a method of life compatible with the strength such a diet affords constitute the guiding principles in the treatment of diabetes. Since insulin does not cure diabetes, but is merely a val-

uable aid in treatment, the education of the family physician and the patient in the intelligent use of insulin is of vital importance. The learning of the essential diabetic arithmetic is a matter of but an hour's study. The diet must not overbalance the drug, else glycosuria will result; on the other hand, the drug must not overbalance the diet, as this may lead to a dangerous reaction. Diabetic coma is a diabetic accident, and, like all accidents, to be avoided.—I. B.

Action of insulin on rats deprived of the suprarenals (*Action de l'insuline sur les rats privés de surrenaux*). Lewis (J. T.), *Compt. rend. Soc. de biol. (Par.)*, 1923, 89, 1118-1119.

The lethal dose of insulin was 10 mgm. per 100 gm. in healthy control rats, while it was only 1 mgm. per 100 gm. in rats deprived of the suprarenals.—T. C. B.

Xanthoma diabeticorum. Major (R. H.), *Med. Clin. N. Am. (Phila.)*, 1924, 7, 1059-1064.

The patient is a married white male, a farmer, aged 33, who was admitted to the hospital for the treatment of diabetes of approximately 18 months' duration. He is a member of a family of 12 children, 5 of whom have had diabetes, 3 dying of the disease. Two weeks prior to admission the patient noticed a rather "profuse" skin eruption over the chest, abdomen, and extensor surfaces of the forearms and thighs. This appeared quite suddenly and simultaneously and was not accompanied by itching or other disagreeable sensation. Examination proved the eruption to be xanthoma diabeticorum, a rare complication of diabetes mellitus. The condition is produced by a deposit of cholesterol, fat and lipid bodies beneath the skin. Successful treatment of the diabetes, including the administration of insulin, resulted in the disappearance of the skin condition.—I. B.

Insulin treatment of the toxemic vomiting of pregnancy. Thalheimer (W.), *J. Am. M. Ass (Chicago)*, 1924, 82, 696-699.

Thalheimer has treated three patients with severe, toxemic vomiting of pregnancy with a combination of hypodermic injections of insulin and the intravenous administration of glucose solution. The results have been striking, and parallel exactly the results in all patients with postoperative acidosis similarly treated. Thalheimer cautions that only pure, tested glucose should be used in preparing the glucose solution. A 10% solution is convenient to use, as with it the patient receives a fair amount of much needed water along with the glucose. The solution should be run in slowly, about 200 to 300 cc. an hour, and it is important that it be kept warm; 1,000 cc. is the amount usually given at a time. About fifteen minutes after the injection is started, about 10 units of insulin is given hypoder-

mically (i. e., 10 of the new U-letin units). At intervals thereafter 10 units is given until for 100 gm. of glucose (1,000 cc. of 10% solution) 30 units of insulin is given. One unit of insulin (U-letin) causes the utilization of from 2 to 3 gm. of glucose, but for safety a slight excess of glucose should be given to prevent a hypoglycemic reaction of insulin shock. It is wise to have epinephrin available for hypodermic use for treatment of a hypoglycemic reaction. Up to the present, however, this has never been needed. Insulin has been demonstrated to have as rapid a curative effect on ketosis and the toxemic vomiting of pregnancy as it has on preoperative and postoperative nondiabetic acidosis. This evidence suggests that the field of insulin therapy may be extended to other nondiabetic conditions.—Courtesy, A. M. A.

**Pancreas hormone and sugar utilization (Pankreashormon und Zuckerverwertung).** Wertheimer (R.), Wien. klin. Wchnschr., 1923, 36, 805.

In normal persons the author found that arterial blood contained much more sugar than venous blood. This proves that the normal tissues use sugar. Whether the tissues burn the sugar or whether they change it into glycogen is not known. In severe diabetes the quantity of sugar in arterial and venous blood is the same. The author then examined dogs before and after extirpation of the pancreas and found that after the operation the difference between arterial and venous blood sugar disappeared. He concludes that the cells require the pancreas hormone to enable them to utilize sugar.—J. K.

**A German insulin.** Zuelzer (G.), Med. Klin. (Berl.), 1923, 19, 1551-1554.

Zuelzer reports that he had an active pancreas hormone which he called Acomatol ready at the beginning of the war, but he did not use it because it produced spasms in dogs. He attributed this to a toxic action of the preparation instead of recognizing it as an indication of its potency. The war prevented further research. He also had the same intention as Macleod to prepare the hormone from the isolated islands of fish pancreas, but the medical faculty of the University of Berlin refused to grant him the means for the necessary journey to Naples. His method of preparation is different from that of insulin. The product is titrated against epinephrin.

—J. Am. M. Ass., 82, 252.

**The size of the parathyroids of rats and the effect of a diet deficient in calcium.** Luce (Ethel M.), J. Path. & Bacteriol. (Edin.), 1923, 26, 200-206.

Rats on a calcium-deficient diet showed a consistent enlargement of the parathyroid gland, which was due to hyperplasia and

not to cell hypertrophy and which increased progressively with the length of time of calcium-deficient feeding. There was no relationship to sex.—Chem. Abst., 17, 2908.

Tetany cured by thyroid and parathyroid transplantation (Nach Epithelkörperchen und Schilddrüsen-transplantation beheilte Tetanie). Maier (P.), Wien, klin. Wchnschr., 1923, 30, 736.

After a goiter operation in a woman of 33 myxedema and tetany developed. She was cured by transplantation of a parathyroid and a piece of thyroid of a horse.—J. K.

Action of parathyroid extract (Einige Beobachtungen über die Wirkung von Parathyroidin). Mandelstamm (M.), Ztschr. f. d. ges. exper. Med. (Berl.), 1923, 35, 370.

Though much experimental work has been expended on the effects of removal of the parathyroids, very little is known of the results of parathyroid hyperfunction, and the few experiments detailed in this paper are therefore of some interest. Rabbits were injected daily with a watery extract of horse parathyroid in increasing doses. The most interesting effect noted was definite protrusion of the eyeball, resembling the exophthalmos of Graves' disease, a result which is rarely produced in animals by thyroid administration. Other symptoms were increased appetite, restlessness, and a heightened excitability to the galvanic current. It is suggested that parathyroid injections produce overaction of the thyroid.

—Med. Sc., 9, 309.

Malignant epithelial thymoma. Report of a case with necropsy. Foot (N. C.) & Harrington (H. H.), Am. J. Dis. Child. (Chicago), 1923, 26, 164-178.

A colored girl 2 years of age had given symptoms for over a year of difficulty in swallowing, paroxysms of coughing and strangling while attempting to drink, but apparently had no pain and no dyspnea except when coughing. The child died suddenly of cardiac failure after being two months in the hospital. Necropsy showed a tumor which was intimately adherent to the chest wall on the left and had forced the left lung downward and backward, compressing it until it was a mere mass of flabby material. Examination revealed it to be a thymoma, which the authors believe to be primary and exhibiting a predominatingly reticular type of growth. They think this is the fifth case of primary epithelial thymoma to be reported and the only one occurring in a child.—M. B. G.

A case of ligneous thyroiditis associated with high-grade dental infection. Bohan (P. T.), Med. Clin. N. Am. (Phila.), 1924, 7, 1069-1074.

The patient was a married woman, aged 38, the mother of 4

living children. The family history was negative. Four months before admission to the hospital there developed a swelling of the neck that increased rapidly in size and became quite tender. She was soon afflicted with spells of coughing, increasing in frequency, accompanied by a sense of suffocation, and with some dyspnea so that sleep was possible only when propped up in bed. There was no dysphagia. There has been a loss of 30 pounds in weight during the past four months, and for over 2 months the temperature varied between  $99^{\circ}$  and  $100.5^{\circ}$  F. The pulse was 104, there was a slight tremor, the eyes were negative, the teeth and tonsils were apparently diseased. The thyroid presented a lump on the left side which did not move on deglutition; the mass was tender, and the area swollen and hard as wool. The leucocyte count was 14,200; the Wassermann test was negative. A tentative diagnosis of malignancy was made. Following temporary improvement under x-ray and other measures, the patient grew steadily worse and marked cyanosis of the face and limbs with dyspnea and crowing inspiration developed 12 days after admission. Operation, with removal of a portion of the mass followed by tracheotomy, resulted in the saving of the patient from death by asphyxia. Pathological examination of the specimen excluded the existence of tuberculosis, syphilis, and malignancy, the final diagnosis being chronic thyroiditis with extensive fibrous encapsulation, in other words, ligneous thyroiditis due to infectious foci. The patient recovered.—I. B.

**Myxedema and mental changes (Myxoedeme et psychose).** Claude (H.) & Bernard (S.). *Encéphale (Par.)*, 1924, 14, 1-2.

A woman, aged 53, had delusions of persecution with terrifying sensory hallucinations, particularly visual; she was very depressed. She had the physical signs of myxedema. Under treatment there was amelioration of the myxedematous state and disappearance of the episode of melancholia. Interruption of the treatment resulted in swelling of the features, lowering of the basal metabolism and recurrence of the mental symptoms.—C. E. N.

**Arteriosclerosis in thyroid deficiency.** Fishberg (A. M.), *J. Am. M. Ass. (Chicago)*, 1924, 82, 463-464.

The case of a patient is reported who presented two seemingly discrete symptom complexes, an anatomic equivalent for each being found at the necropsy. He showed a hypertensive syndrome with a diastolic blood pressure of 35, cardiac hypertrophy and cerebral hemorrhage; corresponding to this there was found at the necropsy generalized arteriosclerosis and beginning primary contraction of the kidneys. Also there was sudden onset of adiposity of a peculiar distribution with retardation of skeletal and more particularly genital development, as well as abnormal distribution of hair. These phenomena point unequivocally to an endocrine disturbance, and at

nercopsy there was found a very extensive atrophy of the thyroid gland, with no other evident anomalies of the endocrine organs. The author thinks it probable that the cardiorenal and endocrine disturbances are correlated.—R. G. H.

**Roentgen-ray therapy in the treatment of exophthalmic goiter.**  
Goodwin (G. M.) & Long (W. B.), *Am. J. M. Sc. (Phila.)*, 1924, 167, 38-54.

The cases selected for this study were of the toxic exophthalmic type. They presented general enlargement of both thyroid lobes and isthmus, the swelling being diffuse and smooth. No case of toxic adenoma is included in this group since there seems to be little doubt that surgery is the proper method of treatment in this type. The roentgen-ray technic employed consisted in the administration of approximately two-fifths of an erythema dose, filtered through aluminum, to alternate sides of the neck each week. A uniform distance of 35 cm. from the target to the skin was used. Filtration was accomplished by 3 mm. of aluminum. The potential at the tube terminals was 140,000 volts, peak, corresponding to a spark gap of 10 inches between points. Five milliamperes were used, and the time of exposure uniformly 5 minutes, with the exception that in highly toxic cases this dose was still further reduced. The report includes 9 cases. In 5 the results of treatment have been satisfactory. In 1 the influence of treatment is doubtful, and in another no conclusion can be drawn because treatment was interrupted. In the 2 remaining cases the toxemia seemed to increase in spite of prolonged treatment. In the 5 favorable cases the authors are unable to speak of the permanency of benefit or tendency to recurrence of symptoms.—*Am. J. Surg.*, 38, 40.

**Exophthalmic goitre in childhood with some unusual manifestations.**  
Heiman (H.), *Am. J. Dis. Child. (Chicago)*, 1923, 26, 216-223.

Heiman gives a review of the literature and adds 3 cases of his own. He concludes that in the light of recent evidence the most rational procedure is to institute first a regimen of strict physical and psychical rest for 6 to 10 weeks. If the patient shows no improvement a short period of roentgen-ray therapy should be tried. Thyroidectomy should be performed if there is no response to roentgen rays. On account of the toxic action on the heart in severe cases it is safer not to wait too long before operation.—M. B. G.

**A shadowgraph method of recording outlines of hands.** Hoeffel (G. N.), *Am. J. Dis. Child. (Chicago)*, 1923, 26, 280-284.

The hand is firmly placed over a sheet of sensitized printing paper (Eastman's velox). A 110 volt, 100 watt Edison Mazda incandescent lamp is then placed 48 inches directly above the middle axis of the hand and the sensitized paper is exposed for 10 seconds.

This procedure should be carried out in a dimly lighted room. The print is then developed with the usual developing and fixing reagents. The relative proportion of the hand of the cretin and of the mongolian idiot show characteristic differences. Although the length of the hands is approximately the same, the length of the palm of the cretin is less than that of the mongolian, while the length of the fingers of the former is decidedly greater than that of the latter.—M. B. G.

**Tuberculosis of the thyroid.** Ito (H.), Chugwai Iji-Shimpo, 1923, No. 1027 (Jan.); Jap. Med. World (Tokyo), 1923, 3, 106.

The author has seen only two other cases of this type reported in the literature, one by Schiller and the other by Pollag. Ito's subject was a 19 year old man. Diagnosis was established by histological examination of the extirpated thyroid. A fistula from the gland developed and through it pus escaped into the subcutaneous tissue, thus forming a cold swelling.—R. G. H.

**Myxedema of the larynx.** Josephson (E. M.), J. Am. M. Ass. (Chicago), 1924, 82, 108-109.

Josephson reports the case of a woman, aged 42, whose chief complaint was orthopnea and a choking sensation in the throat, especially marked when lying flat on the back. The illness dated back to 1913; since then the patient had had a thick voice and had been afflicted with intermittent hoarseness, unaccompanied by cough, which is especially marked in wet weather. Laryngoscopic examination was rendered difficult by an extremely enlarged tongue that filled both mouth and pharynx. Below a large, well developed epiglottis was a mass of tissue springing, apparently, from the posterior wall of the larynx and the interarytenoid space, shutting off the view of the lower structures. This mass was deep red, and seemed to be ulcerated. Thyroid therapy was resolved on; progressively increased doses were given, beginning with one-half grain (0.0324 gm.) of the dried gland once a day, up to 2 grains (0.13 gm.) of the extract three times a day. Within two weeks the symptoms complained of disappeared completely. Laryngoscopic examinations now showed a very large larynx, supermasculine in its proportions, set deep in the throat. Under continued thyroid therapy the tissue of walls and prolapsed ventricle dwindled, leaving a spacious glottis and supraglottic regions. An interesting phase of the treatment was the steady improvement in volume of the voice, parallel to the diminution in size of the tongue, and in its pitch and timbre paralleled to the laryngeal improvement.—Courtesy A. M. A.

**Preliminary report of the Kottmann reaction in children, with a note on the treatment of chorea with thyroid.** Lyttle (J. D.) & Sutton (L. P.), Am. J. Dis. Child. (Chicago), 1923, 26, 179-185.

This study is based upon the observations in 106 cases. In the control group of 28 cases, 21 gave normal reactions. The 3 retarded reactions could be explained upon the basis of medication with sodium bromid and calcium chlorid. Kottmann, Petersen and Merke also found that bromids prolong the reaction. In the group of acute infection 13 were normal, 15 accelerated and 5 retarded. In the group of cardiac children the predominating reaction was acceleration, probably from the lowered vitality of the children. In fifteen choreas the severe and moderate cases consistently showed accelerated reactions. Thyroid was administered with beneficial results in 9 cases. The endocrine and idiocy cases were too few in number to justify any definite conclusion as to the value of the Kottmann reaction; of the 19 in this group, 10 gave normal reactions. In detail, the results obtained were: hypopituitary, 5 normal and 1 accelerated; thymus and microcephalus, 1 normal; cretin, 2 accelerated; hyperthyroid, 1 accelerated and 1 retarded; goiter, 1 retarded; dyspituitary, 1 retarded; idiots, 4 normal, 2 accelerated. Petersen and others in a series of 400 cases obtained markedly retarded reactions in 65 out of 70 cases of hyperthyroidism and in 11 cases under bromid treatment, confirming Kottmann's findings. Petersen considers the reaction a close index of thyroid function and a reflection of the increased metabolism which occurs with hyperthyroidism. An accelerated reaction would therefore be expected with decreased basal metabolism. Kay felt that the reaction failed in cases of hypothyroidism, but that it gave definite indications of hyperthyroid conditions.—M. B. G.

**Hyperthyroidism associated with acidosis.** Major (R. H.), Med. Clin. N. Am. (Phila.), 1924, 7, 1065-1068.

This is the report of the case of a colored female 49 years old whose chief complaints were nervousness, weakness, and loss of weight. Focal infections in tonsils and teeth were present. Three years before, following a severe fright, she became almost paralyzed with exhaustion, and within a few days a "lump in her neck" was observed. When the patient came to the writer's attention she presented a typical picture of exophthalmic goiter, with a basal metabolic rate 53% above normal. Two weeks after admission to the hospital she became irrational and quite toxic; the temperature was 100 F. and the pulse 160 per minute; the blood showed a carbon dioxide tension of 20 volumes percent, and the urine presented acetone and diacetic acid. Under the influence of sodium bicarbonate therapy and a 5% solution of glucose by rectum the patient's condition improved very rapidly. Within 8 hours she became very much less toxic and within 24 hours the evidences of acidosis had disappeared. The author believes that acidosis complicating hyperthyroidism is frequently overlooked.—I. B.



Goiter in the Great Basin. Middleton (G. W.), Calif. State J. M. (San Fran.), 1924, 22, 52-54.

In the Virgin Basin of southern Utah 75% of the women have some form of thyroid enlargement, and in many instances large goiters remain untreated throughout life. In the Salt Lake Valley, on the other hand, due to proximity to saline waters, goiter is a relatively uncommon condition. Treatment depends upon the nature of the thyroid growth. Of the 213 subjects seen and treated by the author, 111 were operated upon; the remainder, largely of the colloid type, were treated nonsurgically.—I. B.

Methods of administering iodine for prophylaxis of endemic goiter. Olesen (R.), Pub. Health. Rep. (Wash.), 1924, 39, 45-55.

Summarizing available evidence Olesen concludes that while numerous methods of supplying iodine for the prevention of endemic goiter have been suggested, the most favored one at the present time is the administration of a chocolate tablet containing 10 mgs. of iodine in the form of an organic acid. One or two of these tablets, according to the age and requirements, should be given each week during the school year to both boys and girls between the ages of 11 and 16. Owing to the presence of thyroid enlargements in children less than 11 years of age, prophylaxis should profitably begin earlier than has ordinarily been recommended. The preventive should be used both in children in whom there is no evidence of thyroid enlargement and in those having such enlargement. In the latter instance, however, the exercise of nominal medical supervision is desirable. The iodine-chocolate combination or other iodine-containing mixtures may be used advantageously during pregnancy, under the direction of a physician. While individual oral administration of iodine is the method generally employed, the use of iodized table salt holds forth considerable promise as an efficient means of preventing endemic goiter in a wholesale manner. However, the difficulties of gauging accurately the dosage and of excluding from treatment the hypersusceptible are manifest handicaps to its uncontrolled application. The wholesale iodization of a municipal water supply may be cited as an ingenious method in need of further appraisal before a definite verdict as to its efficiency can be given. According to the best information available there is little, if any, danger in iodine prophylaxis when it is carried out intelligently. Moreover, the rationale of the procedure is sufficiently sound and the results are sufficiently marked to make its extensive application both justifiable and advisable.—Author's summary.

Th end results of surgery of the thyroid gland. Pemberton (J. deJ.), Arch. Surg., 1923, 7, 37-46.

In 1922 in the Mayo Clinic 1,983 operations were performed on 1,497 patients with goiter with mortality from operation of 0.95%

and by case of 1.2%. Classification of operable thyroid condition is as follows: (1) Diffuse colloid goiter—the common physiological thyroid enlargement in adolescence, producing no symptoms beyond those of pressure, iodine deficiency being the etiological factor. (2) Adenoma without hyperthyroidism. In a small proportion of cases enlargements are entirely concealed in the thoracic cavity. Operative procedure is the only effective remedy. (3) Adenoma with hyperthyroidism. This is not to be confused with exophthalmic goiter. The symptoms of hyperthyroidism usually occur spontaneously and develop gradually but progressively. These symptoms may be induced abruptly by the administration of iodine to a patient with adenoma without hyperthyroidism. The operative mortality is between 2 and 4%. Judd found after 2 years 83% considered themselves cured and 5% more were markedly improved. (4) Exophthalmic goiter. This is characterized by an increased basal metabolic rate, by a peculiar nervous syndrome and usually by exophthalmos, with a tendency to gastric intestinal crises of vomiting and diarrhea. The cause of exophthalmic goiter is unknown, but there is always the characteristic pathologic picture of diffuse parenchymatous hypertrophy and hyperplasia in the thyroid gland. Operation has particular danger just before, during, and following a crisis. In 1922 there were 1,093 operations on 633 patients with exophthalmic goiter in the Mayo Clinic; 11 died; there was operative mortality of 1.005%; by case, 1.74%. Wilson found in the Mayo Clinic 1 case of malignancy in 57. Recent rapid growth in the thyroid suggests malignancy. Wide surgical removal followed by radium or roentgen ray offers the best chance. In a study of 207 cases of malignancy up to January, 1921, the Mayo Clinic gave:

Sarcoma .....	19 cases no cures
Carcinoma .....	62 cases 5%, 5 year cures
Malignant adenoma.....	102 cases 20%, 5 year cures
Malignant papilloma.....	24 cases 33%, 5 year cures
—Am. J. Roentgol., 11, 112.	

Roentgen-ray therapy in thyrotoxicosis; its effect as measured by the basal metabolic rate. Read (J. M.), Calif. State J. M. (San Fran.), 1924, 22, 10-15.

A report of the results of x-ray therapy on all forms of goiter associated with an increased metabolic rate, based upon a series of 50 cases. Although in toxic adenoma operation is a logical procedure, this is far from the case in the treatment of the Graves' syndrome. It is therefore extremely important clearly to differentiate the two conditions prior to the institution of treatment. The roengen ray seems to be effective in at least improving thyrotoxicosis as proved by the reduction in the basal metabolic rate. This is usually accomplished in from 3 to 6 months of treatment.—I. B.

**A relationship of blood sugar to thyroid and suprarenal size in a fraternity of pigeons.** Riddle (O.), Honeywell (H. E.) & Spannuth (J. R.), *Am. J. Physiol. (Balt.)*, 1924, **67**, 539-546.

In a group of brother and sister hybrid pigeons, those with abnormally low blood sugar had large thyroids and large suprarenals. Abnormally high sugar was associated with small thyroids and suprarenals. Less conclusive evidence points to large gonads associated with large thyroids.—T. C. B.

**X-ray treatment of lesions of the thyroid gland.** Williams (J. G.), *Long Island M. J. (Brooklyn)*, 1923, **17**, 353-359.

Toxic adenoma responds readily to the roentgen ray, but surgery is quicker and the mortality in these cases is low. The technique has been to treat the thyroid and thymus areas on each side separately with 4 mm. of aluminum as a filter, a 9-inch spark-gap, at a distance of 9 inches, for 6 minutes to each area. Latterly, where the tonsils showed marked hypertrophy, Williams has included them in the area to be treated, extending the distance to 12 inches and time to 9½ minutes. The second treatment is given 3 weeks later, and a third treatment 4 weeks after the second, the interval between treatments being extended one week longer than each preceding interval. Usually, at the third visit, 7 weeks after the first treatment, there is noted a slowing of the pulse rate and an amelioration of the nervous symptoms. After this, the patient begins to regain some of the previous loss in weight. The eye symptoms and the goiter are the last to show improvement, and frequently do not wholly disappear. The author says that patients treated surgically do better and the risk of operation is less if they had previously had their thymus glands irradiated.—*Am. J. Roentgenol.*, **11**, 103.

# Endocrinology

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THE BEHAVIOR OF THE TESTIS IN TRANSPLANTATION, EXPERIMENTAL CRYPTORCHIDISM, VASECTOMY, SCROTAL INSULATION, AND HEAT APPLICATION.\*

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A realization of the remarkable influences of sex hormones on the differentiation of the genital complex in cattle discovered by Professor F. R. Lillie (1) led him to initiate a concerted program of sex research in the laboratories of Zoology at the University of Chicago looking to the development of our knowledge of the fundamental problems in the biology of sex. The work has been in progress now for some seven years and at the present time is being actively carried forward along many divergent lines.

It was at Professor Lillie's suggestion that I took up the study of some phases of the sex biology of mammals and it is a pleasure to be able at this time to present some of the results obtained from work on the mammalian testis.† While not em-

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\* Read before The Association for the Study of Internal Secretions, eighth annual meeting, Chicago, June 9, 1924.

† The latter part of the investigations here reported have been materially aided by a grant from the committee on sex research of the National Research Council; grant administered by F. R. Lillie.

phasizing directly the aspects of its internal secretions the work deals with many basic problems from which have been built up much of our present-day conceptions of the internal secretions of the testes. I hope the knowledge gained, and the problems discussed, may be of such a nature that a consideration from the viewpoint of this presentation may not appear entirely out of place in a meeting of this society.

Considering first testis grafting, or transplantation, I have only to mention the work of Steinach, Sand, and others whom I will not now name, to recall its importance particularly as it relates to present conceptions of the elements so far believed to be the source of testis hormones. The classical picture of a mammalian testis graft recovered some time after transplantation is given to us as follows: The seminiferous tubules are well outlined by the connective tissue basement membrane, but are usually smaller in caliber than those of normal testes. The content of these tubules consists usually of a single layer of cells located next the basement membrane, the Sertoli cells, often the sole remains of the former germinal epithelium. The tubules, again unlike those of normal testes, are widely separated and the interstices packed with interstitial cells or cells of Leydig and some connective tissue; such a condition of the interstitial tissue has usually been interpreted as an hypertrophy of the cells of Leydig. Since the interstitial tissue is present in an apparent overabundance, the germinal epithelium almost entirely absent, and the Sertoli cells being usually denied a secretory function, many have been led to conclude that the source of the internal secretion of the testis must reside in the interstitial tissue.

I have obtained many testis grafts from rat and guinea pig transplantations that were similar to the above type of graft, but also many that were radically unlike it, and it is to these latter that I would direct your attention for a brief moment. Rat testis grafts have been recovered after transplantation into normal males, castrated males, normal virgin females, castrated females, and females that had delivered normal litters of young, having carried the transplanted testis some months before and during the pregnancy. The idea of the "Antagonism of Sex Hormones" postulated by Steinach to account for his failure

to obtain growth of transplanted testes in females possessing their normal ovaries, and forming the basis of much of his work of the past ten years, as well as the "Atreptical Immunity" hypothesis of the Danish investigator, Knud Sand, formulated to account for the same lack of persistence of testes transplanted subcutaneously into females with ovaries, must, I feel, be discarded. But it is the character of the testis grafts, recovered from subcutaneous, intramuscular, and intraperitoneal positions, I wish most to emphasize.

Many of the grafts, instead of containing seminiferous tubules devoid of germinal cells, have contained tubules with a fairly complete germinal epithelium, many cells of which are in stages of mitosis; two or even three rows of cells may be adhering together sufficiently to build up an epithelium. The curious fact remains, however, that differentiated spermatozoa have never been found in grafts residing in these localities in the animal body. The germinal cells actively divide and produce new cells, but those cells nearest the lumen of the tubule become loosened from the epithelium, escape into the lumen and undergo degeneration. The question is pertinent, Why is not complete germ cell differentiation realized? It has been a problem since first mammalian testes were transplanted to account for the lack of spermatozoa in the testis grafts. Different again from the usual picture of a testis graft the interstitial tissue is not overdeveloped and in fact is not different from that of the normal testis.

A great deal of light has been cast upon the behavior of a graft by a relatively detailed study of experimental cryptorchidism. It has been known for longer than a century that man and other mammals occasionally experience a retention of one or both testes in the peritoneal cavity, one in five hundred military recruits, according to Bevan (2). The structure of such undescended or cryptorchid testes has been described for man, pig, sheep, horse, and other mammals and it is known that not only is bilateral cryptorchidie, or double peritoneal retention of the testes, followed by sterility, but also that such testes are devoid of germinal cells excepting possibly a few spermatogonia; the seminiferous tubule intervals are usually packed with an

apparent over-abundance of interstitial cells. In short, such a testis is quite similar to the usually described testis graft.

The guinea pig, rat, rabbit, and some other mammals retain throughout life a wide open connection between the scrotum and the peritoneal cavity, and by contraction of muscles in connection with the scrotal sac the testes may be elevated through the open inguinal canals into the abdominal cavity, to redescend into the scrotum on relaxation of the latter structure. Under these conditions the testes are normal. If, however, the testes are pushed through the open inguinal canals into the peritoneal cavity and are prevented from returning to the scrotum a very rapid and striking, progressive, degeneration of the generative portion follows. Forceful retention may be accomplished by several slightly different means, i. e., by severing the mesenterial gubernacular connection between the epididymis and the bottom of the scrotum and turning the testis back into the peritoneal cavity; by pushing the testis through the canals and tying the scrotum, or sewing shut the inguinal canals, etc. Under such conditions the blood supply, nerve connections and vas deferens are normal. More certainly will the testis be retained in the abdomen if the inguinal canals are closed with a purse string structure, but in approximately 50 per cent of the cases in the guinea pig the testes do not redescend into the scrotum when the canals remain open, even though the testes are not fastened by sutures.

It makes little difference what means are taken to insure abdominal retention of the elevated testis, the results are the same if the organ does not sag into the inguinal canal. The germinal epithelium of a normal active testis retained for the short period of seven days in the abdomen will be found to be totally disorganized. The usually well defined tubular lumen will be practically filled with a mass of free cells thrown out from the epithelium; many cells may appear approximately normal, but the majority are in a stage of degeneration. Some of the cells can be defined in outline only, others show fragmentation of the nucleus, and chromatin materials scattered throughout the cell or protoplasmic masses may be located in a granular debris, the result of more extensive degeneration. The former compact epithelium is little in evidence, its place

having been taken by a fibrillar reticulum filled with vacuoles or spaces from which the cells have escaped or in which they have undergone fragmentation and dissolution, with or without the complete removal of the fragmented remains.. Very often large multinuclear protoplasmic masses—typical “giant cell” like masses—are to be found either in the epithelial position or loose in the lumen. All stages in the formation of these multinucleate masses can be followed and they are seen to owe their origin to the coalescence of contiguous germinal cells; the cell walls disappear and the epithelium reminds one of the proverbial melting pot in which discrete cells are merged into a common protoplasmic mass.

After fourteen days’ peritoneal retention the majority of the degenerating debris has been removed from the tubules through liquefaction and transportation and but few cells can be seen; these are almost without exception in a degenerate condition. By twenty days little remains in the tubules, aside from the reticulum, than the Sertoli cells situated against the inner border of the basement membrane, and a few spermatogonia. We have, therefore, produced experimentally within twenty days, a typical cryptorchid testis such as occurs in nature.

So long as the testis remains in the peritoneal cavity it is degenerate. Followed at brief intervals from seven days to more than a year after operation, the testes are found to decrease progressively in size; tubules shrink to one-third their original diameter and interstitial cells become more prominent and are collected in masses between the now more widely separated tubules. If by chance the testis returns to the scrotum after being elevated into the peritoneal cavity it may be found a few months later in a normal condition. If descent has been only partial, and the testis is held by adhesions from taking its normal scrotal position, then the testis may be in part normal, part degenerate. In general it may be stated that the more nearly a testis returns to its normal scrotal position the more nearly normal will be the seminiferous tubule epithelium.

To test the powers of recuperation of a testis after degeneration, both testes of an animal were elevated to the peritoneal cavity and so retained for twenty-four days. By a second operation one testis was replaced in the scrotum, the opposite one



removed and studied histologically to ascertain the stage of degeneration of the one in the scrotum. The seminiferous tubules, at the end of twenty-four days are empty of all degenerating remains, and Sertoli cells with a small number of spermatogonia form a single layer of cells against the walls of the basement membrane.

It can be realized, therefore, that the testis replaced in the scrotum, after its twenty-four days' retention in the abdomen, was in a highly degenerate condition. It was allowed to remain in the scrotum for  $2\frac{1}{2}$  months, when the animal was killed and the testis prepared for histological study. The replaced testis had almost completely recovered from its degenerated condition. The majority of the tubules contained a well established epithelium and in many of them spermatozoa had again appeared, and these tubules were normal. A few tubules were in stages of partial recovery, but some were entirely devoid of epithelium. In the latter case it is questionable if recovery would have ever taken place and there is little doubt that all cells capable of further division were destroyed during the peritoneal confinement. The few totally degenerated tubules were located indiscriminately among normal tubules and not segregated off into any particular locality, thus showing that recovery had no definite relation to particular local conditions within the gonad, but depended upon the presence of cells capable of further division at the time of scrotal replacement.

It follows, therefore, that the scrotum exerts a peculiarly striking influence upon the testis and an influence that is necessary not only for the complete differentiation of germ cells but even for the retention of cells previously differentiated. Removed from the scrotum, or from conditions stimulating those of the scrotum, a testis is rapidly deprived of its germinal epithelium.

Is this not a partial solution for the absence of differentiated germ cells in testis grafts? With a realization that the testis-scrotal relationship is necessary for the production of spermatozoa I transplanted testes into the scrotum by sewing them to the walls of the tunica vaginalis. The idea proved correct for I have recovered testis grafts, from transplantation onto the scrotal walls six months previous, that contained normal semi-

niferous tubules with differentiated spermatozoa. Thus for the first time have testis grafts of mammals been obtained that contained normal seminiferous tubules. We have additional evidence in this result that the scrotum is necessary for germ cell differentiation in those mammals that normally possess a scrotum.

Approaching the general problem of testis reactions, this time following the effects of occluding the outlet duct or vas deferens by ligation, sometimes combined with resection of the duct, we discuss a problem that has been a point of controversy for more than fifty years, a controversy dealing not with a general interpretation of a series of phenomena but merely with the question whether testicular degeneration follows ligation of the vas deferens. Opinions in number are about equally divided between degeneration and lack of it, but due to the great influence of Bouin and Ancel (3), really the founders of the conception that the testicular hormones are derived from the interstitial cells, it has in late years been assumed that the problem was settled and that vas deferens ligation caused the testes to degenerate. The contrary contentions of earlier workers were dismissed by these two investigators, on the basis of observations made before a sufficient length of time had elapsed after vas deferens ligation. Following Steinach, the testes undergo degeneration, perhaps regenerate in many cases, but interstitial cell hypertrophy follows and we are asked to believe that rejuvenation and restoration of youthful qualities is accomplished by the operation; supermales are considered possible merely upon the basis of a great interstitial cell hypertrophy. Bouin and Ancel state that if one waits sufficiently long degeneration invariably follows vas deferens ligation. It should be noted, however, that in the absence of a definition of a *sufficient length of time* the statement cannot be disproved; degeneration undoubtedly follows in old age, and it is generally accepted that the sexual life of a rat and guinea pig is to be counted in a small number of years. With the above assertions Bouin and Ancel reproduce a drawing of a guinea pig testis 78 days after vas deferens ligation that was totally degenerate as concerns the germinal epithelium. Seventy-eight days should, therefore, be a sufficiently long time to wait for degeneration. In our lab-

oratory Dr. Oslund found that vas deferens ligation of ten months' duration in the rat and guinea pig was followed by perfectly normal testes (4). Some degenerate testes did occur in Oslund's material, but by no means sufficiently related in time intervals after operation to be due to the influence of the blocking of the vas deferens. Knowing the rapidity of degeneration with inguinal or peritoneal retention of the testes, he was able to correlate all cases of degeneration with an abnormal scrotal relationship of the testis, where the position of the latter was definitely noted at the time of its removal. An appreciation of the delicate relationship established with, and dependent upon; the scrotum leads to the belief that the instances of degeneration of other workers are due to testicular retention by adhesions in the inguinal canals or peritoneal cavity, or by some influence that removes the testis from its normal relationship with the scrotum.

I believe that if one appreciates the fact that a given number of animals having the vas deferens completely blocked for a period of, for example, four months, possess normal testes, but operations on the same type of animal in the hands of other workers result in degenerate testes in one-half the given time, we must conclude that degeneration is actually due not to the operation itself but to subsequent influences due in reality to other factors.

With the assistance of Mr. W. J. Quick I have recently studied the effects of vas deferens occlusion in the rabbit, an animal often employed for a study of this problem (5). We have studied the testis histologically from thirteen days after complete occlusion of the vas deferens (a time according to Steinach where degeneration takes place followed by regeneration) to longer than six months after the operation. During this period of time the seminiferous tubules are perfectly normal, the germ cells are in active mitosis and quantities of spermatozoa are present. Vas deferens occlusion does not cause the testes to degenerate in the rabbit within six months after the operation. Can we offer an attempt at a logical explanation of degeneration obtained in other laboratories? Oslund's work would appear to do so. It thus appears that displacement of the testis in reference to the scrotum, a situation not fully appreciated hereto-

fore, may account for a number of such cases. To compare with a testis having the vas deferens occluded, we have purposely allowed the opposite testis of an animal to exist with an abnormal scrotal relationship but with the vas deferens normal, i. e., not occluded. The former testis at the end of thirteen days is perfectly normal, whereas, the one with normal vas deferens but with abnormal scrotal relationships presents a testis lacking from one-half to three-fourths of the germinal epithelium, lost through degeneration but with many of the remaining cells in a stage of mitosis. Is not such a testis, thirteen days after operation, in a condition that would easily fit the contentions of Steinach (6) or Tiedje (7) of a degeneration followed by regeneration? Surely the testis is highly degenerate, and just as certainly are mitotic figures abundant and the condition could easily be construed as regeneration changes. But here the vas deferens had not been occluded and we know that the influences were due to displacement from the normal scrotal environment. Adhesions following operation will bring about just such a result; they have sometimes been formed after our operations and have been mentioned by Sand.

But what of vas deferens occlusion of longer duration? In the twenty rabbit testes of our materials enlargements at the cut end of the vas deferens (spermatocysts), described by Oslund, Tiedje, and Sand and considered by some as a deterrent of testis degenerations, have never occurred. At three and one-half months after vasectomy and later, our materials have presented a pronounced and striking enlargement of the epididymis, the result of hypertrophy of this structure and due undoubtedly to the stimulus of the presence of testicular products brought to it from the continuously active seminiferous tubules. The epididymis at six months after vas occlusion has been noted to be twice or even three times its normal size. It is so large that one may detect immediately, on a superficial glance at the scrotum of a living rabbit, which one of the two testes has had the duct blocked; the contour of the epididymis impresses itself upon that of the scrotum due to its great distension.

Since a large part of the epididymis is located at the bottom of the scrotum, underneath the testis proper, and since the scrotum itself does not enlarge correspondingly, the effect is to dis-

place the testis upward into the open inguinal canal or even into the peritoneal cavity. The testis once having been forced through the canal into the abdomen is returned to the scrotum less easily than the normal testis with a smaller sized epididymis. One of our cases was found partially confined to the peritoneal cavity and here the testis was degenerate. Obviously it would be a misrepresentation to attribute this degeneration to vas deferens occlusion.

It is interesting to note the results of vas deferens occlusion reported by Sand (8). Fifteen cases of vas occlusion were reported, some having been observed one year or longer after the operation. Two cases only are reported as degenerate and thirteen in which no degeneration had occurred, yet Sand states a confirmation of Bouin and Ancel that vas ligation produces degeneration; he states, however, that often a year is not sufficiently long to wait for degeneration. Is it not time to reverse our conceptions and conclude that vas deferens ligation does not of itself produce degeneration of the testis?

The unsuspected intensity of epididymal hypertrophy is worthy of additional remarks. Spermatogenetic activity has continued without evidences of arrest after the excurrent duct of the testis has been ligated. The products resulting from this activity, if permitted to accumulate in the tubules would be expected to produce an arrest of development, perhaps of degeneration, on account of abnormal pressure. It is particularly interesting to realize that the normal currents directed outward from the testis proper to the epididymis, functioning normally for the transportation of spermatozoa, perhaps also of certain secretions, are of sufficient intensity to overcome the resistance of a filled epididymis and an internal pressure great enough to cause a doubling or tripling in size of the latter structure. The tubules, despite their activity and despite the backward pressure from the epididymis, are not filled with the products of their own activity, but these products are removed into the reservoir provided by the epididymis. Miss van Wageningen (9) has recently confirmed Steinach that ligation between the epididymis and the testis produces degeneration, perhaps through pressure atrophy; she also declares degeneration after vas deferens ligation. From our own materials, however, *vas*

*deferens occlusion in rabbits does not produce degeneration up to six months after operation if the testes retain their normal scrotal relationships*; Sand has shown that degeneration does not follow even after a year; Oslund failed to obtain it up to ten months; Shattock and Seligman (10) on sheep found normal testes one year after the operation; numerous clinical reports on man show normal testes several years after vas deferens occlusion; and I have shown that normal tubules are present even in testis grafts. Since a single factor or condition to be operative should express itself within a time equal to one-half the sex life of an individual animal, we should conclude, I believe, that vas deferens ligation of itself does not produce degeneration of the testis.

It will be understood that this operation, the so-called Steinach operation, is practiced on the human individual for a supposed tuning up of a wornout organism. The significance of the testis reactions following vasectomy as described by Steinach can be weighed briefly in two considerations: First, in the many cases of vasectomy performed in our laboratory on guinea pigs, rats, sheep, and rabbits no single case has ever occurred where interstitial cell hypertrophy followed as a result of this operation; and it should be remembered that this is the only morphological basis upon which Steinach's regeneration rests. Second, should an hypertrophy follow, it would remain to be proved that a mass of interstitial cells in the testis represents a corresponding quantitative intensity in the production of internal secretions.

But to return again to known facts what factors, may we ask, are the causes of the rapid and striking degeneration of the testis when it is displaced from its normal scrotal environment? I have shown above that a delicate and necessary relationship exists between a normal germinal, or tubular, epithelium and the scrotum. What are the factors operative in causing complete disorganization, within seven or eight days, and ultimate degeneration of all germinal cells when the testis is kept in the peritoneal cavity?

Having eliminated every factor that came to mind as a cause of the degeneration excepting one, I stated in 1922 (11) that a differential body temperature was suspected as the causal

factor. Taking note of a similar suggestion by Crew in the same year (12) that body temperature might be the cause of the lack of spermatozoa in undescended testes my idea was strengthened and experiments were designed to test the hypothesis. If it is a higher temperature of the body cavity that causes degeneration, then scrotal temperatures should be lower than peritoneal temperatures, and the scrotum would serve as a local thermo-regulator. It should then follow that by preventing the scrotum from functioning in this hypothetical manner the testes should degenerate while located in their normal position.

With the co-operation of Dr. Oslund the scrotum of a ram was insulated against loss of heat by securely, though loosely, encasing it in woolen materials and a water-proof covering, sewed to fit the scrotal contour, and suspended sufficiently by artificial supports as to preclude binding the scrotum or producing abnormal pressures (13). Within eighty days the testes were found to be devoid of spermatozoa; many tubules were in advanced stages of degeneration, the tubules being filled with loosened, degenerating cells similar to peritoneally retained testes, while many tubules lacked entirely the germinal epithelium. *The animal had sterilized itself with its own body heat due to prevention of the local thermo-regulatory function of the scrotum.*

With Mr. W. J. Quick, temperature readings were made with ordinary thermometers passed into the abdomen through locally anaesthetized abdominal regions of rats, rabbits, and guinea pigs (14). One thermometer bulb in the peritoneal cavity and another passed through the open inguinal canal into the scrotum, alongside the testis, showed us that at the same moment the scrotal temperature was appreciably lower than that in the peritoneal cavity in all cases. The differences between the two cavities varied as the external environmental temperature varied. Thus in a white rat observed in a room temperature of 16°C. the scrotal temperature was 8°C. lower than that of the peritoneal cavity. This gives absolute proof, therefore, that the normal environmental temperature of the testes is appreciably lower than the general body temperature.

There remained for disposal one further assumption to provide actual proof of the correctness of our working hypothesis:

the testis should undergo degeneration following the application of temperatures slightly higher than those normal for it.

It was found that hot water pads applied to the external surface of the guinea pig scrotum, raising the temperature approximately  $6^{\circ}$  to  $7^{\circ}\text{C}.$  above normal body temperature for a period of fifteen minutes resulted in severe tubular degeneration within ten days after application (15). Increasing or decreasing either the length of application or the degree of temperature applied we can produce at will any stage of degeneration desired from the destruction of a few peripheral tubules to complete degeneration of all seminiferous tubules in the testis. Direct submergence of the testis in a controlled saline bath of  $47^{\circ}\text{C}.$  for five minutes is sufficient to produce complete degeneration of every tubule of a guinea pig testis within five days after the application. Thus the application of temperature slightly higher than its normal is shown to be fatal to the generative portion of the testis and the degeneration following such an application is very similar to the type occurring after testis elevation into the peritoneal cavity.

The totally independent work of Fukui (16), a Japanese investigator, but recently published, arrives at a similar interpretation with respect to the effects of temperature on the testis and the explanation of degeneration of testes elevated into the body cavity. Applying heat in the form of hot water, hot air, heat of the sun, and arc light heat Fukui has worked out a so-called "heat curve" of the testis in relation to time of application and degree of temperature employed. A very striking observation, however, and one that greatly strengthens our proof of degenerate testes when elevated into the body cavity was made as follows: Fukui elevated both testes of an animal into the peritoneal cavity but artificially cooled the external area on one side in the region of the elevated testis. He found that in the course of a few days the testis in the artificially cooled area was normal, whereas the uncooled testis was highly degenerated. Thus with all the accumulated evidence there should no longer be any doubt that our conception of the effects of the body temperature on the testis condition is the correct one.

Let us examine briefly, then, the qualifications of the scrotum as a local thermo-regulator for the testes. In its simple



form in the rodent the scrotal sac is but an outpouching of the peritoneal cavity posteriorly underneath an area of skin much thinner than ordinary skin, and well provided with sweat glands; the muscular layers are exceedingly thin; subcutaneous fat is absent, and the organ varies in size and shape as environmental temperatures vary. Thus on hot days the scrotum relaxes to its full pendent condition permitting the testes to be farther removed from the body, whereas in a cold atmosphere the scrotum is contracted, bringing the testes nearer to the body. It is difficult to differentiate a male from a female rat in low temperatures without close scrutiny, as the testes may be so elevated on scrotal contraction that their position is in reality abdominal; on hot days, however, the testes protrude considerably in a post-anal position. A similar adjustment follows also for man.

The physical and physiological principles of a local temperature regulator are inherent in the mechanism, and in consideration of all proofs brought forward I have no hesitancy in stating that *the scrotum of mammals is now to be considered a local thermo-regulator for the testes and that the regulatory or functional capacities are indispensable for the production of differentiated germ cells or the maintenance of those already produced*. Not longer than three years ago Cunningham, in his book *Hormones and Heredity* (17), stated that "Various causes have been suggested for the formation of the scrotum, but no one has ever been able to suggest a use for it" (page 147). I believe we have not only been able to suggest a use for it, but have proved its function and utility.

Objections may be raised against the idea, however, due first to the lack of such a structure in the bird, where the testes are abdominal and the body temperatures even higher than that of the mammal; and second to the lack of it in some mammals (monotremes, elephant, many aquatic forms, bats, etc.). In regard to the first objection may I not state that the bird and mammal are entirely two different animals. Many structural and physico-chemical differences exist between these two forms. Because the testicular tissue is a decidedly heat labile substance in one is no good reason for assuming it in the other; slight physico-chemical differences may produce an entirely different

reaction system, and we need not be troubled by such physiological differences, particularly when we appreciate the many structural differences between the two animals. As regards the mammal it need only be mentioned that most biologists now assume that an evolution of animal forms has occurred within the class mammalia as well as among vertebrates as a whole, or invertebrates. In the monotremes, the lower reptile-like mammals in which it is said body temperatures are by no means constant but are subject to wide variations, the testes are located in the reptilian position—namely, just posterior to the kidneys in the abdomen. As we ascend the scale of mammals a typical scrotum is gradually produced. In some mammals (bat, sloth, etc.) the testes have descended into the pelvic region and have taken up a position against the anterior abdominal wall in a pouch-like depression over which the skin is very thin. It is unquestioned that sufficient temperature adjustment is thus obtained, else we would not have such animals preserved for our edification. In rodents an onward step has been made; the testes protrude into the outpouching of the peritoneum in the inguinal region, but the final scrotal condition has not yet been accomplished as the sacs present a wide open connection capable of permitting passage of the testis into and out of the abdomen. The final closed scrotum is gained only in the higher mammals. It should not trouble us exceedingly that variations have occurred during its evolution—adaptations perhaps—for such have been present even in the evolution of such typical structures as appendages.

We may therefore assume a gradual evolution of a scrotum within the mammal group and may we not, with all justice, consider that perhaps the evolution of the entire mammalian group may have been more or less dependent upon this scrotal evolution? It involves certainly the capacity of the reproductive system to function and therefore the very foundation of the race.

While adding little actual accomplishment to solving the riddle of the internal secretion of the male gonad I believe the fundamental reactions of the testes under the varying conditions discussed, and the attempt at an explanation of the tissue reactions, will give a point of departure from which a more rational interpretation of observed facts may proceed.

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# A QUANTITATIVE STUDY OF THE HUMAN HYPHYSIS CEREBRI, OR PITUITARY BODY\*

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MINNEAPOLIS

While the general size and appearance of the normal human hypophysis is generally well known, this organ has become of such clinical importance that more accurate data are necessary especially on the limits of normal variability, not only of the organ as a whole but also of the size and histological appearance of its various parts. It may be well to recall that the pituitary body is a complex structure composed of pars anterior (pars distalis), pars nervosa (processus infundibuli or pars posterior), pars intermedia (juxtaneuralis or pars infundibularis) and pars tuberalis (an epithelial extension along the under surface of the tuber cinereum or floor of the third brain ventricle). Most of these are shown in Figure 1, as seen in horizontal section. These various portions apparently differ functionally and must, therefore, be evaluated independently.

While there are thousands of weights of the main portion of the gland as a whole, there are no accurate figures on the mass of the various subdivisions. Even the weight and dimensions of the whole organ as recorded are not so reliable as they might have been because it is not clearly indicated how much of the surrounding connective tissue (dura mater) and of the infundibular stalk is included. The stalk represents about 5% of the whole organ, but may reach 8%. The dural sheath about the hypophysis may easily be as much as 25% of the weight of the gland. In our material we have dissected off practically all the dura, leaving only the thin capsule or pial covering as shown in Figure 1. The pial sheath cannot be removed without removing with it some of the gland parenchyma. The stalk we have

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cut off as short as possible because in the ordinary autopsy only a portion is left attached to the rest of the gland and there was no means at hand for determining how much was still connected with the brain.

#### TECHNIQUE

The method employed in obtaining the original data here presented has already been described and published in detail (Rasmussen and Herrick, 1922). It is sufficient here merely to state that serial sections of whole undamaged normal organs

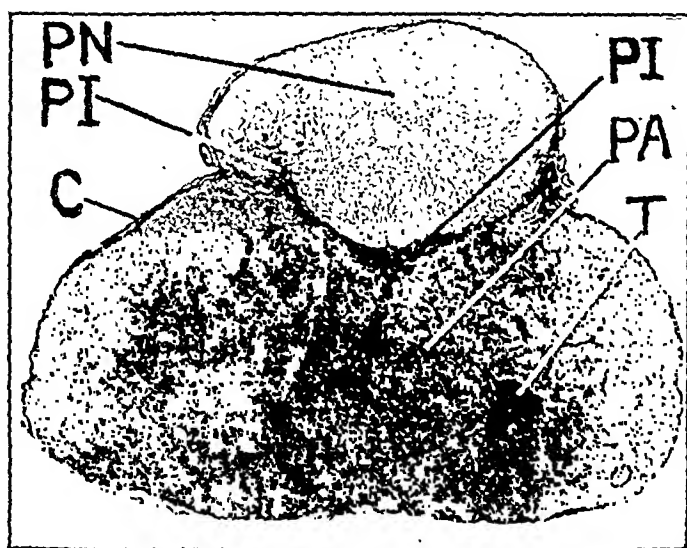


Figure 1. Photograph of a horizontal section of a typical normal human hypophysis to show the regions involved in this report as well as the amount of capsule or connective tissue left on the gland. C, Capsule; PN, Pars Nervosa; PI, Pars Intermedia; T, Trabecula; PA, Pars Anterior.

were projected at a magnification of 20 diameters (surface area magnification of 400) upon heavy paper which has a fairly constant weight per sq. cm. The various subdivisions of the gland were outlined with a fine hard pencil or ink and then cut out. The relative weight of the paper representing a given part of the organ gives the necessary data for determining the weight of that part in the fresh gland if the weight of the whole fresh gland is known and if the specific gravity of all parts is the same and the histological technique causes equal shrinkage of all parts. The differences in specific gravity are negligible for all practical purposes and the shrinkage is fairly uniform (Rasmussen and

Herrick, 1922). So if the combined weight of the pieces of paper representing, say, pars nervosa is 20% of the weight of the paper representing the whole gland and the fresh hypophysis weighed 0.5 grams, then the nervous lobe weighs 20% of 0.5 grams, which is 0.1 of a gram.

TABLE I  
WEIGHT OF HUMAN HYPOPHYSIS CEREBRI

Authority	Date	No. of Cases	Age in Years	Weight in Grams				Remarks
				Male	Female	Both Sexes	Extremes	
Schönmeyann	1892	9	20-46	612			400- 700	None normal after 50 years.
		2			975		600-1 35	
Bryce and Beadles	1893	50	22-78	453		527	130- 712	Insane
		50	31-84		600		384- 896	
Comte	1898	33	22-70	Non-preg	.480		392- 885	None normal after 50 years.
		6	21-39	End of preg.	911		540-1 265	
Caselli	1900	50	Adult	667				Mostly mental cases
		50	Adult		731			
Launois	1904	50	Aver. = 50½	588 but only	480 if cereb. hemor is excluded			11 cases cerebral hemorrhage = 755
		50			601			
Latreille	1908	6	44-60	615			350- 800	
		15	22-68		705		400- 950	
Archard-Loeper	1908	7	Adult			500		
Halliburton, Candler, Sikes	1909	18	Adult	469			4 over 500	Asylum material
		24	Adult		567		4 under 50	
Creutzfeldt	1909	110	Various			Both sexes	900-1 800	Increases till 30. Decreases after 50
Erdheim and Stumme	1909	92	21-70	612			400- 920	30-40 years = 643 (23 cases)
		13	21-50		.665 (Nullipara)		400- 890	
		39	21-84		745 (Unknown)		350-1 050	
		38	21-40		847 (Primipara)		360-1 130	To 58 years post-partum
		73	Adult		865 (Multipara)		530-1 450	2-16 children

#### WEIGHT OF THE WHOLE HYPOPHYSIS

Table I gives a summary of the most important data found in the literature on normal or nearly normal human adults as well as our own determinations.

Some additional data were not tabulated for various reasons. Thus Parski (1901) and Testut (1912) give weights which were

excluded because they were far too low to be representative. Livon (1909) also gives a rather low average (0.442) without stating the number, sex or nature of the material. Cutore (1910) has a table of 25 weights, but only 6 of these are adult and they died of various diseases. On the other hand, Schönemann (1892) excluded many cases from his list of normals that others would

TABLE I—(Continued)  
WEIGHT OF HUMAN HYPOPHYSIS CEREBRI

Authority	Date	No. of Cases	Age in Years	Weight in Grams				Remarks
				Male	Female	Both Sexes	Extremes	
Lucien	1911	100	20-85	.500-.710			500- 710	Change after 50 is not pathological
			20-80		.570-.970		.570- 970	
Kolde	1912	3	20-34		1.113 (Just post-partum)		.740-1.700	1-5 children
Tolken	1912	38	18-70+			.540		
Munson-Shaw	1914	?	Adult			.540		
Simmonds	1914	800	16-20	688	701			Not certain that pregnant females were excluded
			21-30	733	801			
			31-40	741	814			
			41-50	687	.775			
			51-60	666	798			
			61-70	660	.754			
			71-80	697	730			
			81-90	599	755			
Rössle	1919	132	Soldiers	.627				712 if stature is 175 cm. and over
Petersilie	1920	189	Soldiers	621			300- 900	
Krieger	1920	30	Adult	580				
Rasmussen	1923	50	19-65	560			.400- 855	Stalk and dura removed

have included. He selected only 11 out of 89 adults as being absolutely normal, considering no hypophysis normal after 50 years of age. Seventy-eight of the 89 were excluded by Schönemann for one or the other of the following four reasons: chromophilic changes in the chief cells (30 cases), overgrowth of connective tissue in the stroma of the anterior lobe (32 cases), blood vessels too abundant (9 cases), too much colloid (7 cases). Incidentally, it may be noted that the figures so often quoted from Schönemann as representing the average adult weight in reality include many children hypophyses. In order to avoid errors of

this kind, the original publications have been consulted in every case except two.

Many measurements of the three diameters accompany the weight of the organ, but since it is the bulk of the tissue that we are primarily interested in and not its exact shape, these measurements have not been included for consideration. In passing, it may be noted that the average hypophysis of about 0.6 grams in weight is in the neighborhood of 13 mm. in transverse diameter, 10 mm. in sagittal diameter and 6 mm. in vertical diameter (see e. g. Erdheim and Stumme, 1909; Tölken, 1912; Thom, 1901; Zander, 1896).

#### (a) SEX DIFFERENCES

It will be noticed in Table I that when the sexes are separated, the female hypophysis is noticeably heavier than the male. This difference is slight in nullipara (Erdheim and Stumme). In pregnant females and in women who have borne children the hypophysis may be expected to be distinctly larger (Comte, 1898; Erdheim and Stumme, 1909; Kolde, 1912). Thoan (1907) and others have similarly recorded this difference during pregnancy. Erdheim and Stumme plotted a curve which shows that there is an increase in hypophyseal weight to the 10th lunar month of pregnancy and then a rapid decline. Their data, as well as some other incidental observations, indicate also that repeated pregnancies result in a still larger hypophysis in many cases. If the 72 cases discarded as normals by Schönemann (1892) (for doubtful reasons as already explained) be separated according to sex, the 41 male hypophyses averaged 0.710 grams as compared with 0.745 grams for 31 females.

The average for our series of 50 perfect hypophyses from adult males, who met sudden accidental death in most cases, is somewhat lower than the figures given by others. This may be due to the fact that we remove the dural covering, leaving only the thin capsule of pia mater, and cut off the infundibular stalk before the weight is taken. This seems the only logical procedure with ordinary autopsy material. As already explained, the method of dissecting out the gland may then make as much as 33% difference in the weight. For this reason it is not justifiable to combine the data given by the different writers, since they are



not specific enough as to what is included and what is excluded.

We have not been able to get enough normal female hypophyses to check carefully with the male series.

### (b) AGE DIFFERENCES

The extensive data given by Simmonds (1914), particularly, indicate that the hypophysis is largest from 20 to 40 years of age and that in the male it tends to decrease markedly in old age. Also in our own data, as shown in Table VI, the group between 35 and 45 years of age has the highest average weight, while the oldest group (46-62 yrs.) has the smallest average weight. This is not due to a difference in stature, for the group with the highest weight incidentally happens to have the smallest average stature, which would tend to annul the age differences, as will be seen from what follows.

### (c) RELATION OF HYPOPHYSEAL WEIGHT TO STATURE

The principal figures relating to stature have been collected in Table II.

TABLE II  
RELATION OF WEIGHT OF HYPOPHYSIS TO STATURE

Authority	No. of Cases	Stature (cm.)	Weight of Hypophysis (grams)	Remarks
Rössle.....	?	175 and up	.712	As compared with .627 when all heights (132 soldiers) are included
Petersilie.....	13 36 61 53 14 8	Under 160 161-165 166-170 171-175 176-180 181-185	.566 .580 .646 .632 .718 .723	Total cases 185 soldiers.
Rasmussen.....	10 10	159-173 173-192	.537 .652	20-45 years of age.

This is interesting because of the influence of the functional activity of the hypophysis to gigantism. In general this organ may be expected to be larger in tall than in short men. It has been repeatedly shown that no such correlation exists between adult body weight and weight of the hypophysis. Since the hypophysis of old men tends to decrease distinctly in size, we eliminated from our cases all those above 45 years so as to have more uniform material, and then divided them into two equal

groups according to stature (see Table II). The ones with statures below 173 cm. had a distinctly lower average hypophyseal weight than the other group with statures above 173 cm.

(d) RELATION OF THE WEIGHT OF THE HYPOPHYSIS TO  
THE SIZE OF THE SELLA TURCICA

From numerous studies on the fossa hypophyses (Zander, 1896; Fitzgerald, 1910; Gibson, 1912; Cope, 1916; Johnston, 1917; Jaugeas, 1918; Howe, 1919; Jewett, 1920; Enfield, 1922; Mintz, 1922; Gordon and Bell, 1922; Camp, 1923; Knox, 1923),

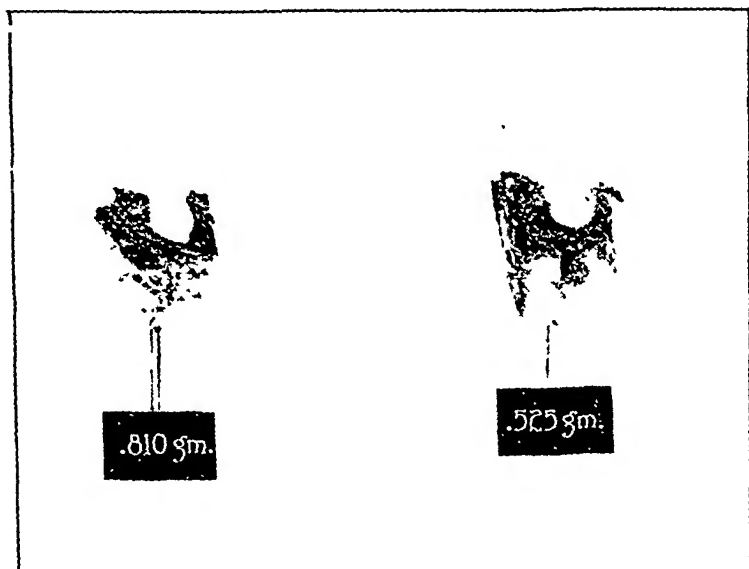


Figure 2. Photograph of two normal hypophyseal fossae with the weight of the hypophysis taken from each to show the discrepancy that may exist between the size of the sella and the hypophysis.

it is evident that it varies greatly in size and shape in normal individuals. Since the hypophysis was frequently received in situ with the sella intact, it was incidentally noticed that there may be a wide variation between the bony compartment and the weight of the inclosed hypophysis—a fact which has already been fully appreciated by some clinicians (e. g., Timme, 1919). There are still those, however, who are prone to stress too much the importance of the size of the sella. A good illustration of

the discrepancy which may exist is shown in Figure 2, which is a photograph of two normal sellae, but slightly under average dimension, with the weight of the corresponding hypophysis attached. Although the cubical space in these two sellae is almost the same, the hypophysis in one (0.810 grams) was 50% larger than the hypophysis in the other (0.525 grams). In fact, an x-ray picture of the one containing the larger hypophysis would have given no suggestion that the hypophysis was extreme in size for a normal male. The amount of surrounding connective

TABLE III  
WEIGHT OF PARTS OF HUMAN HYPOPHYSIS  
MALE—ADULT 20-34 YEARS OF AGE

Autopsy No			20-276	20-405	20-372	20-252	20-279	20-44	22-205	20-146	22-327	22-80
Age			20	22	24	25	29	31	31	32	32	34
Pars Ant (Dist )	Trab	G	0020	0007	0005	0020	0015	0050	0022	0036	0017	0011
		%	32	14	09	34	36	1 06	30	76	28	17
	Paren	G	4266	4024	4253	3089	3274	3460	5683	3473	4302	5330
		%	69 37	79 52	75 40	69 95	79 28	73 62	76 28	72 36	71 70	84 33
	Total	G	4286	4031	4258	4007	3299	3510	5705	3509	4319	5341
		%	69 69	79 66	75 49	70 29	79 64	74 68	76 58	73 12	71 98	84 50
Pars Nerv		G	1042	0367	1109	1210	0516	1000	0525	0876	1436	0743
(Pror Infun )		%	16 95	7 25	19 66	21 39	12 51	21 28	7 05	18 25	23 94	11 75
Pars	Collod	G	0338	0511	0022	0029	0150	0030	0060	0002	0011	0035
		%	5 50	10 10	39	50	3 63	64	80	05	18	55
Inter (Juxt )	Paren	G	0022	0008	0017	0014	0028	0041	0036	0014	0039	0075
		%	35	17	31	24	67	87	48	30	65	1 19
	Total	G	0360	0519	0039	0043	0178	0071	0096	0016	0050	0110
		%	5 85	10 27	70	74	4 30	1 51	1 28	35	83	1 74
Capsule		G	0162	0143	0234	0132	0147	0119	1124	0397	0192	0127
		%	7 51	2 82	4 15	7 58	3 56	2 53	15 09	8 28	3 25	2 01
Whole Gland		G	615	506	561	570	413	470	745	480	600	632
Stature (cm )			175	162	182	173	170	181	189	160	173	192

tissue and above all the capacity of the intercavernous sinus vary greatly and account for the difference between the size of sella turcica and hypophysis. For these meningeal relations of the hypophysis consult Koller (1922), Hughson (1922) and Cowdry (1922).

THE VOLUME OF THE CHIEF SUBDIVISIONS OF THE HYPOPHYSIS

Only general statements regarding the proportion of the various parts of the human hypophysis have been found in the literature. The outside measurements of the anterior lobe and the posterior lobe that have been published give no adequate or accurate idea of volumes. In Tables III, IV and V are recorded our findings in thirty selected cases. The autopsy numbers refer to the files of the Department of Pathology, University of Minnesota. The three age groups are compared in Table VI.

TABLE IV  
WEIGHT OF PARTS OF HUMAN HYPOPHYSIS  
MALE—ADULT 35-45 YEARS OF AGE

Autopsy No.		22-295	22-329	22-332	20-323	20-291	20-380	22-344	22-218	21-280	22-266
Age in Years		35	35	35	36	36	37	40	40	43	45
Pars.  Ant.  (Dist )	Trab.	G	0012	0018	0026	0043	0010	0032	0008	0014	0016
		%	15	26	33	84	24	49	15	29	26
	Paren.	G	5435	4714	5379	3832	332	4501	4113	2824	4048
		%	70 58	68 45	72 21	72 30	76 87	68 20	78 36	59 46	66 36
	Total	G.	5447	4762	5405	3875	3338	4533	4121	2838	4064
		%	70 73	68 71	72 54	73 14	77 11	68 69	78 51	59 75	66 62
Pars Nerv.		G	1150	1687	1522	1120	0816	1538	0750	1366	1458
(Proc. Infun.)		%	14 94	24 05	20 43	21 13	18 84	23 30	14 30	28 76	23 9
Pars  Inter.  (Juxt )	Colloid	G.	0019	0064	0025	0046	0032	0022	0039	0033	0032
		%	25	92	34	86	74	33	74	70	53
	Paren	G	0013	0032	0076	0022	0045	0110	0034	0024	0201
		%	17	46	1 02	42	1 03	1 67	64	51	3 29
	Total	G.	0032	0096	0101	0068	0077	0132	0073	0057	0233
		%	42	1 38	1 36	1 28	1 77	2 00	1 38	1 21	2 82
Capsule		G	1070	0406	0422	0234	0099	0389	0306	0489	0345
		%	13 90	5 86	5 67	4 42	2 28	5 90	5 82	10 28	5 66
Total Weight		G	770	693	745	530	433	660	525	475	610
Stature (cm )			174	160	170	171	160	174	168	159	175

From Table VI it will be seen that the pars anterior represents about 72% of the total organ, pars nervosa 18%, pars intermedia 2%, and the capsule 8%. The amount of capsule varies somewhat with the ability to dissect away the dura. In some cases, especially in older individuals, it tends to adhere to the posterior surface. In general it cannot be completely removed from the interlobular sulcus without danger of tearing

stances that a particular colloid mass is actually in the intermediate portion; but since it is usually impossible to exclude this possibility it was thought best to include the doubtful colloid masses with pars intermedia. The colloid in the residual lumen (between pars intermedia and pars anterior) is also included. The globules of colloid found distinctly in pars anterior are in general too small to be seen with the magnification employed and have, therefore, not been considered. Their combined volume would not influence the values significantly.

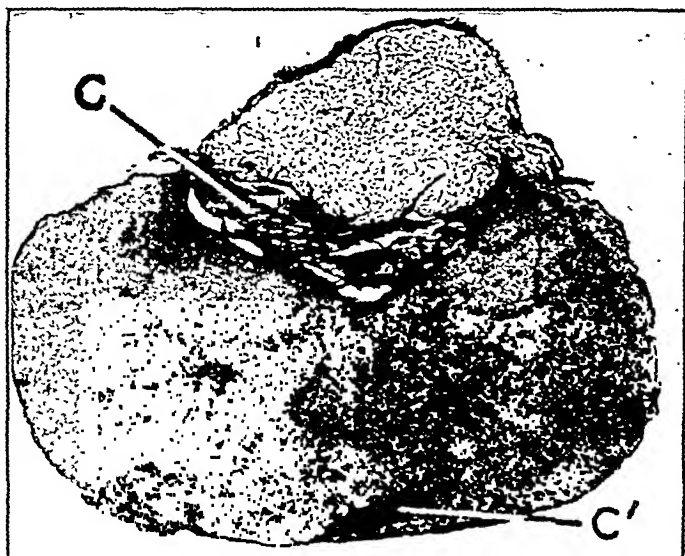


Figure 3. Photograph of a horizontal section of a normal male hypophysis containing an unusually large amount of colloid. Autopsy 20-276. C, Colloid which tends to chip in cutting, one piece (C') having been carried away out of place.

The first two cases listed in Table III had an enormous amount of colloid. In No. 20-408 it amounted to over 10% of the entire hypophysis and more than pars nervosa, and yet these were apparently perfectly normal men. Figure 3 shows a photograph of a section of the hypophysis of No. 20-276, in which over 5% of the entire hypophysis is colloid.

When it comes to the parenchyma of pars intermedia, only an approximation of its volume is claimed, because the cells are frequently irregularly scattered about in pars nervosa (Fig. 1). Greater accuracy could be obtained by using a much higher magnification so that even a single cell could be outlined. This would, however, increase the amount of work all out of propor-

tion to the returns. As Tables III, IV and V show, the weight of the parenchyma of pars intermedia varies so much relatively that nothing is gained by an extended discussion of so short a series of cases.

In connection with the discussion that is going on about the functional significance of this part of the gland, attention may be called to the fact that if it were rounded up it would make a sphere only about 2 mm. in diameter weighing only 0.005 grams in an average adult man.

TABLE VII  
THREE CASES OF NON-NEOPLASTIC POST-ADOLESCENT HYPOPHYTARISM  
COMPARED WITH 30 NORMALS

Autopsy No.			22-368	22-246	22-81	Average of 3 Cases	Average of 30 Normals
Age			36 Years	58 Years	59 Years		
Weight			250 Lbs.	223 Lbs.	330 Lbs.		
Pars Anterior	Trabeculae	G.	.0023	.0021	.0022	.0022	.0025
		%	42	40	34	39	45
	Parenchyma	G.	.3927	.3397	.4678	.4001	.4008
		%	70 75	64 09	75 45	70 10	71 36
	Total	G.	.3950	.3418	.4700	.4023	.4033
		%	71 17	64 49	75 79	70 48	71 81
Pars Nervosa		G	.1076	.0882	.0939	.0966	.1031
		%	19 38	16 64	15 15	17 06	18 37
Pars Intermedia	Colloid	G	.0027	.0010	.0101	.0046	.0064
		%	48	18	1 63	76	1 18
	Parenchyma	G	.0017	.0053	.0074	.0048	.0052
		%	30	1 00	1 20	83	88
	Total	G	.0043	.0062	.0175	.0093	.0116
		%	78	1 17	2 83	1 59	2 06
Capsule		G	.0481	.0938	.0386	.0602	.0447
		%	8 66	17 70	6 22	10 86	7 76
Weight of Whole Gland			G.	.555	.530	.620	.563
Stature (cm.)			173	178	189	180	172

THE HYPOPHYSIS IN POST-ADOLESCENT HYPOPHYTARISM  
OF BOTH LOBES

Table VII gives the results of an analysis of three additional cases which had the typical physical features of so-called non-neoplastic bilobar postadolescent hypophyitarism, according to the classification of Engelbach (1920) and Tierney (1923).

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## CONCLUSIONS BASED ON A STUDY OF FOUR THOUSAND CASES OF GOITER\*

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The material on which the conclusions in this paper are based consists of four thousand surgical and non-surgical cases of goiter which I have observed during the past five years at the Jackson Clinic and as a Fellow in Goiter Surgery at the Mayo Clinic. Although these observations are for the most part not new, they are culled from a great mass of facts and for the first time formulated in brief statements.

Advanced cases of exophthalmic goiter are at times treated as endocarditis by heart specialists, as nervous dyspepsia by gastroenterologists, and as neurosis by neurologists.

Little discrimination is made between cases of adenoma of the thyroid with hyperthyroidism and exophthalmic goiter. They are all too generally called "toxic goiter."

The study of goiter is complex, and much confusion exists over the diagnosis and treatment of the various forms. To bring order out of this chaos of opinion, a simple classification is essential, for example:

1. Colloid goiter.
2. Adenoma.
  - (a) With hyperthyroidism (toxic adenoma).
  - (b) Without hyperthyroidism (simple adenoma).
3. Exophthalmic goiter (Basedow's or Graves' disease).
4. Tuberculosis, malignancy, syphilis, thyroiditis, actinomycosis, and so forth.

The usual text book classification of goiter is confusing. The various clinical types of cystic, calcareous, and hemorrhagic goiter are merely degenerative forms of adenoma.

\*This paper is a part of the study of goiter which were already appeared in *Annals of the American Association for the Study of Goiter*, June, 1924, Vol. 70, pages 840 to 844, and is republished by the courtesy of that journal.



## COLLOID GOITER

Colloid goiters appearing at puberty are seen in 60 per cent of girls between the ages of sixteen and twenty in the goiter district of the Middle West.

Factors in the etiology of colloid goiters are: A deficiency of iodine in the soil and consequently in the drinking water; an excessive demand upon the thyroid gland for thyroxin by the muscular, osseous, and especially the reproductive systems at puberty; an undue mental and physical strain imposed upon the thyroid by modern scholastic requirements and social obligations.

The ordinary colloid goiter with its soft globular feel and symmetrical enlargement is easily diagnosed. The vascular type with thrills and bruits, pseudo-exophthalmos, tachycardia, and nervousness must be differentiated from exophthalmic goiter by the absence of true exophthalmos, quadriceps loss, or severe loss in weight. A normal basal metabolic rate confirms the diagnosis of colloid goiter.

In the treatment of colloid goiter, three common mistakes are:

1. The diagnosis is too long delayed and treatment is begun too late.
2. There is no uniformity in the method of treatment.
3. Treatment is continued in spite of the development of large adenomas.

Colloid goiter may be prevented by administering 10 mg. of sodium iodide once a week during the school year, as proved by Marine and Kimball.

The treatment of colloid goiter should be begun early, since adenomas tend to develop between the ages of sixteen and twenty.

The vascular type of colloid goiter responds most favorably to thyroid extract or thyroxin. Iodine gives better results in the ordinary type.

Apparently adenomas develop in neglected colloid goiters as a form of compensatory development. Consequently the incidence of adenoma of the thyroid is decreased by the prophylactic treatment of colloid goiter.

## ADENOMAS OF THE THYROID

Adenomas rarely cause symptoms of hyperthyroidism before the age of twenty-five, unless provoked by iodine medication.

One in every four adenomas becomes toxic before the patient reaches fifty years of age.

One in every five adenomas develops a substernal projection.

Five women have adenomatous thyroids to every man that has one.

An adenoma is present an average of sixteen years before the onset of toxic symptoms.

The onset of toxic symptoms is both more gradual and insidious in adenoma than in exophthalmic goiter. Toxic symptoms exist an average of four years before the patient with an adenomatous goiter consults a surgeon.

The slowly progressive hyperthyroidism of an adenoma causes permanent and serious damage to the heart and kidneys. Myocardial degeneration, as evidenced by irregularities in heart rhythm and edema of the ankles, is of frequent occurrence.

The popular interest which has been aroused in the treatment of goiter by iodine has greatly increased the number of cases of iodine hyperthyroidism. Iodine is a specific in the prevention and cure of colloid goiter of adolescence, providing no adenomas are present. If in doubt of the presence of an adenoma of the thyroid, do not give iodine.

Thyroidectomy is indicated in the majority of patients more than twenty-three years of age with adenomas of the thyroid.

In adenoma of the thyroid the gland is asymmetrically enlarged, and one or more nodular tumors may be palpated. In exophthalmic goiter the gland is symmetrically enlarged.

In toxic adenoma acute crises do not occur. Thrills and bruits are rare. Exophthalmos is not seen. The average age of the patient is forty-four years. Hypertension and a disproportionately high diastolic pressure is the rule. The basal metabolic rate averages plus 38 per cent. Loss in weight and strength, tremor, nervousness, a moist skin, tachycardia, and palpitation occur as in exophthalmic goiter.

Lugol's solution and ligation are not indicated in the treatment of toxic adenoma.

I give two hypodermics before all operations, gr.  $\frac{1}{4}$  of morphine, followed in fifteen minutes by gr.  $\frac{1}{300}$  of scopolamin.

#### ANAESTHESIA

Because of the numerous advantages of the novocain method of local anaesthesia, I use it in 90 per cent of cases.

The operator and his assistants must handle the tissues most gently and carefully to minimize the sensation of pain and pressure.

Any trauma or injury to the recurrent laryngeal nerve may at once be detected by talking with the patient.

When the operation is finished, undetected bleeders may be found by causing the patient to cough and strain.

The disagreeable postoperative nausea and vomiting following ether narcosis are eliminated.

The risk of postoperative hyperthyroidism is diminished.

There is a decreased chance of postoperative aspiration pneumonia, although pneumonia may occur.

The operator can tell whether the patient's condition warrants continuing the operation.

The disadvantages of novocain anaesthesia are:

Increased strain on the surgeon.

Increased psychic disturbance to the patient.

Increased time required for operating.

#### OPERATION

Team work, rather than individual brilliancy on the part of the surgeons, favors a rapid, bloodless resection of the thyroid gland.

Time may be gained by preventing hemorrhage from the small vessels in dissecting up the skin and platysma, by applying a very sharp scalpel edgewise and not too deep, while strong traction is exerted by assistants on either side of the flap.

Opinions differ on the necessity of dividing the sternohyoid and sternothyroid muscles. Unquestionably it gives better exposure, and whenever this is required as in the case of a vascular, friable exophthalmic goiter or a large colloid adenoma, there should be no hesitation about dividing the muscles.

Early exposure and anaesthetizing of the upper poles, followed by double clamping and dividing, permits better mobilization of the gland, reduces the factors of shock and pain, and decreases hemorrhage.

Having properly exposed the goiter by dissecting with the scalpel along the plane of cleavage, one should ligate the lateral veins in order that these vessels may not be torn away and retracted into the wound.

The recurrent laryngeal nerve must be avoided by placing clamps parallel and not at right angles to it. Only the edges of the capsule or the surface of the gland are sutured.

#### POSTOPERATIVE CARE

Postoperative patients must be kept under the influence of morphine for from twenty-four to forty-eight hours, depending on the degree of toxicity. Fluid intake must be kept up to 3500 c.c. Digitalin, gr. 1/25 hypodermically, may be given every hour if indicated.

Eighty-five per cent of the cases of toxic goiter are cured by surgery. Medical measures may temporarily benefit but only delay the relief possible to obtain by surgery. Roentgen ray and radium are contra-indicated in the treatment of any type of goiter except exophthalmic goiter. In these cases treatment must be continued over a long period of time with only uncertain results.

# HETEROACTIVITY OF THE PITUITARY GLAND WITH HYPERTHYROIDISM. DISCUSSION OF THE SYNDROME AND REPORT OF AN ILLUSTRATIVE CASE.

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## INTRODUCTION

The great divergence of opinion regarding clinical classifications of diseases of the pituitary gland, is largely responsible for the confusion existing in the literature. Some few writers still retain the original classification advanced by Cushing, others, with a somewhat commendable but hardly progressive conservatism, are still willing to admit only such outstanding syndromes as gigantism, acromegaly and dystrophia adiposogenitalis to the category of definitely classified pituitary disorders, and place all other manifestations under the general nebulous heading of dyspituitarism. In addition to this barrier we are further handicapped by finding many reported cases in which the histories and data are too meager to permit reclassification.

The anatomico-physiological classification of Engelbach and Tierney (1) is not only well in accord with established experimental data, but has been elaborated by the evidence gained from a careful clinical study of over 200 cases of pituitary disorder. While it must be admitted that this classification will undoubtedly undergo changes as our knowledge on the subject increases, it now forms the best working basis for the further study of these cases. As their classification is to be utilized in the presentation of this case, it seems advisable to give a brief outline of it, at least in so far as it is pertinent to the features of this case.<sup>1</sup> They consider that the two lobes of the pituitary gland have certain well defined and separate functions, the anterior lobe mainly governing skeletal growth, development and

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1. No attempt is made to outline the whole classification.

function of the sexual organs and the development of the secondary sex characteristics. The posterior lobe chiefly affects body metabolism. Either one or both of these lobes may become hypo- or hyper-active, or one may be in a hyper-secretory state while the other is under functioning (heteroactivity). The clinical syndrome produced depends largely on whether this altered function takes place before or after the completion of skeletal growth, especially in anterior lobe disorders.

Preadult hyperactivity of the anterior lobe gives rise to an individual with increased skeletal growth or even a giant. Gigantism, however, is not necessarily a result; the individual may simply be large and well proportioned. While this overgrowth affects all bones, it may not affect them equally, so that Engelbach and Tierney recognize three types of stature, i. e., the *normal*, in which the length of the torso is equal to the length of the lower extremities and the span of the arms equal to the height; the *acromegalic type*, in which the torso is longer than the lower measurement and the span less than the height, and in which other signs of acromegaly (slight prognathism, etc.) may be present; the *eunuchoid type*, in which the lower measurement is greater than the torso and the span greater than the height—all three types simply depending on whether the long bones of the extremities have grown the same, more or less than the short and acral bones (vertebra and facial bones).

In the *normal type* (exemplified by the present case) the head is large but in proportion to the body, and the features are well balanced. The hands and feet, while large, are also well proportioned, and radiographs show slight mushrooming of the terminal phalanges. The genitalia and sex glands are normally or even over-developed, and the sex functions, libido, potentia and menstruation are normal as long as the hyperfunction is maintained, but are totally or partially lost if the function changes to under activity.

The posterior lobe has little or no effect on skeletal growth so that we may find signs of its disorders in a person of any of the above types. Since hypofunction of the posterior lobe gives rise to a more definite chain of events than hyperfunction, and is considered to be the cause of the cardinal symptoms in this case, only this phase of its altered function will be considered.

In pure posterior lobe hypofunction, uncomplicated by any other endocrine disorder, the disturbances are mainly metabolic and include the following: low basal metabolism,<sup>2</sup> increased carbohydrate tolerance, low blood pressure, subnormal temperature, slow pulse, atonic constipation, girdle and mammillary adiposity, great fatigability, general malaise, headaches, and, at times, anomalies in the secretion of urine (diabetes insipidus). As in other diseases we do not expect to find all of these signs and symptoms present in every case, and it must also be remembered that other endocrine glands may become secondarily involved and greatly complicate the picture.

It is very important from the standpoint of diagnosis to emphasize two rather well-known facts. *First*, those cases which begin as a hyperfunction, especially of the anterior lobe, either before or after adult life, have a remarkable tendency to later pass into a state of hypofunction, which may involve either the anterior or posterior lobe alone or in combination; so that the signs of acromegaly or gigantism may be accompanied by every feature of hypofunction, and it is only by a careful analysis of the altered functions and by correlating their presence with the physiology of each lobe that a correct diagnosis can be made. *Second*, definite alterations in the shape and size of the sella turcica are found only in those cases where a pituitary neoplasm is responsible for the altered function. A possible exception to this statement will be referred to later.

#### THE CASE

*Miss F. R. Single. American. Age 21.* The patient was formerly employed as a stenographer, but has recently been unable to work for any length of time because of her condition. She was first seen by the writer July 21, 1922, at the Out-Patient Dispensary of the Barnes and Jewish Hospitals, and was sent from here to the Jewish Hospital for observation.

*Chief Complaints* were: (1) great fatigability and general malaise; (2) dizzy and fainting spells; (3) loss of weight; (4) constipation; (5) pain and tenderness in the right iliac fossa; (6) very severe and constant headaches.

*Family History.* The patient is the youngest of three living children. One brother died suddenly in infancy, cause unknown. The

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2. While reduction in basal metabolism is sometimes found, it is by no means constant, and Dr. Engelbach now considers its presence or absence of little consequence in the diagnosis of posterior lobe hypofunction. (Personal communication.) There is no question that changes in metabolism do occur, as evidenced by the fat deposition, but these changes may produce little or no alteration in oxygen consumption. When there is a marked deviation of the basal metabolism from normal, its cause should be sought for in the thyroid function.

father, brother and one paternal uncle are very tall and slender and of eunuchoid types. The family history is otherwise negative.

*Menstrual History.* Menstruation began at the age of thirteen. The periods have been regular every 28 days since the onset, and of three or four days' duration. *The onset of the present symptoms caused absolutely no change in them.* She has always had slight dysmenorrhea, but she is sure that it has not been aggravated by her present trouble.

*Past History.* The subject had the usual childhood diseases. She had scarlet fever in early childhood and a severe attack of typhoid fever at the age of twelve years. She has always been tall for her age, and *grew so rapidly that at fourteen she had practically reached her present size.* She thinks that she has grown very little in height since then, but that her hands and feet have enlarged. She had influenza in 1918. In June and July, 1918, she was confined to bed because of pain in the right iliac fossa, which was diagnosed as appendicitis. In November, 1918, appendectomy was performed. The patient states that the appendix was not ruptured and that no drains were used. A few months after the operation she began slowly to develop dragging and pulling pains in the right iliac fossa. Until about one year ago the patient was in perfect health and was fond of skating and other outdoor sports, but has been unable to participate in them since the onset of her present symptoms.

*History of the Present Illness.* The patient has not been feeling well for about one year, but the symptoms for which she now seeks relief have had a duration of about six or eight months and have been getting progressively worse. In the early fall she weighed 140 pounds, but has been slowly losing weight and now weighs 126 pounds. About six months ago she began to have fainting spells. She usually feels weak and short of breath before these attacks come on, but there is no definite aura. Loss of consciousness is not complete, but she usually falls and is not able to protect herself, but so far has not been injured. There is no coma following the attacks, and after a short rest she is able to continue her work. These spells are more apt to come on when she arises from a sitting or recumbent posture, and have occurred about once every two or three weeks. She fainted twice the week before entering the hospital. There is no tinnitus aurium preceding or during the attacks. Whenever she arises from a sitting or recumbent posture she becomes dizzy and faint, and frequently has to sit down again to recover her balance before walking. These dizzy spells have no definite rotatory nature and she never has them when she is lying down. She always has a tired, languid feeling and is easily fatigued by even slight exercise. She does not feel sleepy or fall asleep during the day, but is mentally inert. She sleeps well at night, usually for eight or nine hours, but feels tired in the morning. Ordinary walking is not accompanied by dyspnea, but walking upstairs causes some breathlessness. Several months ago she noticed that her feet would swell slightly during the day and that her shoes would feel too tight at night, but this has been absent for the last month or more. She has never noticed any definite edema. The headache is present on arising in the morning and continues all day; in fact, she is seldom free from it, at times even waking up at night with it. It is very severe and throbbing in nature, is felt principally deep between the temples, and is made worse on change of posture. The pain in the right iliac fossa developed slowly some months after appendectomy. She describes it as dragging and pulling in type, "like something was attached to the skin." This sensation is especially marked when lying on the left side. It is not influenced by menstruation or defecation, but is worse after walking or running. She has suffered from slight constipation for several years, but it has



been getting progressively worse during the last year, and for about two months before entering the hospital she was unable to have a bowel movement without a cathartic or enema. She never has a vomiting attack. There is no nocturia, polyuria or painful micturition, no cough or night sweats, and no polydipsia. The appetite was fairly good until about two months ago, but for about two weeks before entering the hospital she felt too miserable to eat and took only a little tea, toast and fruit.

#### PHYSICAL EXAMINATION JULY 23, 1922

The patient is very tall and thin, with muscular development about proportional to the size. There is marked kyphosis in the upper lumbar region. The hands and feet are very large. She appears very miserable, and when she arises from the recumbent to the sitting or standing posture her distress is evident. The facial expression, movements and attitude all indicate a feeling of severe general malaise. She answers questions quickly and intelligently. The complexion is sallow; the mucous membranes are not especially anemic. The skin is warm and moist. She weighs 126 pounds.

*Measurements* were as follows: (1) from vertex to middle of symphysis pubis, 88 cm.; (2) from middle of symphysis to floor, 88 cm.; (3) height, 176 cm. (5 feet 10.4 inches); (4) span of arms, 175 cm.

*Head.* The head is large but well formed and in proportion to the body. The hair is fine and thin. The scalp is negative. There is no pain on light percussion of the skull, and no mastoid tenderness. There is slight equal tenderness over both supraorbital notches. The nose is large, with pointed tip and straight bridge. The malar bones are prominent. The lower jaw is prominent, with slight tendency to prognathism. The teeth are in good condition, no crowding, the upper incisors large and lateral occlusion good. The pharynx and tonsils are negative. The tongue is large and protrudes in mid line. The pupils are dilated but equal and regular; they react normally, showing hippus. The movements of eyeball are normal. There is very slight lagging of the upper eyelids. There is no exophthalmus.

*Neck.* Rather marked pulsation is seen in the suprasternal notch. There is slight systolic bruit over the carotids. There are a few small, hard lymph glands near the greater cornu of hyoid bone and posterior to the sternomastoid. No distended veins are observed. *The isthmus of the thyroid is visible and palpable, and the neck is full in the region of the two lobes.* The gland is soft, however, and contains no palpable masses. There is no abnormal pigmentation around the face or neck.

*Thorax.* The thorax is long and narrow, but well formed. The costal angle is acute. Litton's sign is present on both sides. The breasts are small, well formed and virginal in type. The hair distribution is normal. The cardiac findings are negative in regard to size, rate, rhythm and sounds. The respiratory movements are equal and regular. Tactile fremitus is normal. The percussion note is of normal resonance throughout. Breath sounds are normal except in the right apex posteriorly, where they are probably more bronchovesicular than normal, and in the left apex posteriorly, where there are a few soft crepitant rales which disappear after coughing and deep breathing. Vocal fremitus is normal except in the left apex posteriorly, where it is slightly increased.

The chest was again examined about one week later by Dr. Albert Taussig, and these signs, in the apices posteriorly, were found to have disappeared.

*Abdomen.* The abdomen is slightly scaphoid. It moves normally on respiration. There is an old appendectomy scar. There is no

abnormal hair or fat distribution. The pubic hair line is straight. There is a very marked cutaneous vasomotor reaction in the chest and abdomen, which consists of a deep red line appearing every time the skin is gently stroked. This line appears immediately and stays for a long time. The abdominal reflexes are hyperactive but equal on both sides. There is no rigidity or tenderness above the umbilicus. The liver and spleen are not palpable. There is marked cutaneous hyperalgesia between the appendectomy scar and the umbilicus, but not over the scar itself or below it; protective muscle spasm is also present in this region. There is little or no pain on deep pressure in this region, most of the hyperalgesia being cutaneous. The supra pubic region is negative.

*Extremities. Upper.* Axillary hair is normal. There is no abnormal hair distribution on the arms. The axillary and epitrochlear glands are not palpable. The biceps and triceps reflexes are normal. The hands are very large, with wide wrists, but well proportioned. The fingers are long but neither tapering nor clubbed. The nails are of normal size and not brittle; lunar markings are prominent. There is a coarse, gross tremor of the extended arm and hand, but no fine tremor of the fingers or hand. *Lower.* No abnormal hair distribution is seen. The knee and ankle reflexes are equal and normal. The feet are large and well proportioned. The toes are long, the nails normal.

*Vaginal Examination* (7-23-22), Dr. R. S. Tilles. The external genitalia are well developed. The hair distribution is normal. The outlet is nulliparous. The vagina is normal. The cervix is slightly softened and points downward and backward. The uterus is forward and somewhat larger than normal. The fundus is long and narrow, lies behind the symphysis pubis, and can be felt here on abdominal examination. Between the cervix and fundus there is a definite area of softening, which finding in the presence of a different history would resemble a sign of pregnancy. The adenexal region is negative. The culdesac is empty. *Diagnosis:* The pelvic condition is negative and does not account for the general symptoms.

January 8, 1923. A second vaginal examination was made on this date (five and one-half months after the first examination). The pelvic conditions were essentially the same, so that the possibility of a pregnancy can be definitely eliminated.

*Ear, Nose and Throat Examination.* No pathological condition was found to account for the loss of weight and headaches.

*Blood Pressure.* Determinations were taken in the recumbent position. The systolic pressure was found on several occasions to vary between 100 and 114 mm., and the diastolic between 68 and 80 mm. The pulse pressure was always about the same, being between 30 and 35 mm.

#### SPECIAL AND LABORATORY EXAMINATION

*Urine* (single uncatheterized specimen.) The urine is acid. Albumin, sugar and diacetic acid are negative. Acetone is positive. Many W. B. C. were found, R. B. C. rarely, and no casts. The acetone was probably due to starvation acidosis and disappeared after the patient was put on a sufficient diet.

*Blood. Cytologic.* R. B. C. count is 3,640,000; W. B. C., 11,200; Hb., 70%; polymorph., 74%; small mono., 24%; large mono., 2%; Eosino., 0%; Baso., 0%. The stained smear is normal. *Wassermann.* The test is negative in both alcoholic and cholesterinized antigens. *T. B. Comp. Fixation.* Negative.

*Chemical.* Non-protein nitrogen is 42 mg. For the carbohydrate tolerance, see Chart 1.

*Basal Metabolism.* An average of three separate determinations which were well controlled and checked gave plus 23 per cent.

*Temperature.* The temperature on admission to the hospital was 99.4°. For a period of 21 days following this, the morning, evening and occasional noon temperatures were found above normal only five times. These rises occurred at different times of the day, and only once reached 99.5°. For the remaining 16 days the readings were between 97° and 98.6°, and for six days during this time the temperature was constantly subnormal.

*Pulse.* The pulse rate ranged between 60 and 80 during the 21 days of observation.

*X-ray Examination.* *Chest.* The lung fields, including the apices, are clear. The diaphragm moves fairly well. The angles are clear and sharp. Hilus shadows are slightly fused. The heart and vessels are narrow. The heart is of vertical type. *Cecal Region.* No evidence of adhesions are found. *Hands.* The hands have long phalangeal bones, the terminal ones showing slight mushrooming. The carpal and metacarpal bones are somewhat enlarged. *Sella Turcica.* This structure is somewhat small; the clinoid processes appear normal; otherwise negative.

## POSTURAL BLOOD PRESSURE CHANGES, JULY 24, 1922

<i>Posture</i>	<i>Systolic</i>	<i>Diastolic</i>	<i>Pulse Pressure</i>	<i>Pulse Rate</i>
Lying .....	110	80	30	73
	114	78	36	72
Sitting .....	102	84	18	101
	104	80	24	100
Standing .....	98	78	20	132
	98	80	18	120

The striking drop in systolic pressure, producing cerebral anemia, is one explanation for the fainting and dizzy spells caused by changes of posture. The fact that the diastolic pressure remains practically constant indicates that the peripheral resistance in the arterioles is more or less perfectly maintained. The fall in systolic pressure can be partially accounted for by the combination of visceroptosis and sparsity of extra peritoneal and omental fat, which, combined, allow a fall in the intra-abdominal pressure when the upright posture is assumed, with a consequent momentary stagnation of the blood in the portal system and large abdominal veins. This explanation, however, does not account for the persistent low systolic pressure in the recumbent posture or its relation to the endocrine dyscrasia.

## GOETSCH TEST, JULY 25, 1922 .

<i>Time</i>	<i>Systolic</i>	<i>Diastolic</i>	<i>Pulse Rate</i>
Before .....	100	68	68
	102	70	68
Three min. after injection of 0.5 cc. of 1-1000 Adrenaline Cl....	148	86	93
6 minutes .....	142	84	76
9 minutes .....	134	80	72
12 minutes .....	130	78	72
15 minutes .....	130	68	78
18 minutes .....	128	66	72
21 minutes .....	120	70	72
24 minutes .....	118	66	72
27 minutes .....	116	..	80
39 minutes .....	118	68	80
45 minutes .....	118	68	80
55 minutes .....	118	68	72

Subjective signs and symptoms consisted of increase in the headache, marked pulsation in the vessels of the neck, marked pallor, sighing respirations, and slight tremor. Proper precautions were taken to eliminate the psychic element. The test is considered positive.<sup>3</sup>

#### PITUITRIN TEST, JULY 30, 1922

Time	Intestinal Cramps	Nervous Symptoms	Pallor
Three min. after 1 cc. of Pit. (S) in- tramuscularly ..	absent	none	no increase
6 minutes .....	absent	none	pos. slight incr.
8 minutes .....	very slight	none	no increase
11 minutes .....	absent	none	no increase
16 minutes .....	absent	none	slight incr.
23 minutes .....	absent	none	no increase

This test was originally used by Engelbach and Tierney to determine the presence and degree of posterior lobe insufficiency. They found that a much larger dose was required to give the intestinal reaction (cramps followed by evacuation) in cases with definite posterior lobe insufficiency than in normal individuals. They later decided that while the above was true in some cases, it was not constant enough to allow definite conclusions to be drawn from it.

An interesting feature in this case is the fact that the first test was entirely negative, but after the patient was put on treatment a gradually decreasing tolerance was noted, so that after a short time 1 cc. of Pituitrin (S), intramuscularly, produced intestinal cramps and evacuation, and several months later definite intestinal cramps were obtained with 0.5 cc.

#### DIFFERENTIAL DIAGNOSIS

*Early Pulmonary Tuberculosis.* This was one of the first conditions to be considered. The symptoms in general are characteristic. However, the negative x-ray and physical findings in the chest, negative compliment fixation test, absence of cough, laryngeal symptoms, night sweats, and daily temperature elevations, and finally the excellent response to treatment, seem to be sufficient to rule out this condition.

*Neurasthenia.* As our knowledge of medicine in general and endocrinology in particular increases, those obscure symptoms formerly united under the heading of neurasthenia are gradually being unraveled, and from them tangible entities are being established. The general reactions of this patient, her former excellent health, the absence of etiological factors, and the positive evidence of markedly deranged metabolism which returned to normal as her symptoms abated under treatment, are certainly sufficient to eliminate this diagnosis.

3. The value of the Goetsch test in the diagnosis of hyperthyroidism is very doubtful. It has been reported positive in many cases which showed no other evidence of hyperthyroidism, so that a negative test assumes more importance than a positive one. It has been included here, with a full realization of the questionable value, simply to give complete data.

*Ménierè's Disease.* The attacks of vertigo are in no way characteristic of this condition and it can be dismissed without further explanation.

#### ENDOCRINE DYSCRASIAS

*Hypogonadism.* The patient's size and general development might at first sight make this diagnosis seem reasonable, but a careful analysis of the findings absolutely eliminates it. The most important evidence against this diagnosis is the normal development of the external genitalia, uterus, ovaries, secondary sex characters, and the fact that menstruation began at the usual age and has continued normally until the present time.

*Adrenals.* There is no absolute evidence that hypofunction of the adrenals exists. The low blood pressure, asthenia, etc., while characteristic of this condition, are equally characteristic of hypofunction of other glands, especially the posterior lobe of the pituitary. While most writers claim that these syndromes are pluriglandular and usually involve the adrenals, the excellent response to pituitary treatment in this case shows that if hyposecretion of the adrenals does exist it is secondary, and is at least partially rectified by restoring the normal pituitary balance.

*Pituitary.* Since the two lobes of this gland have such widely different functions, it is necessary to analyze them separately.

*Anterior Lobe.* In this case there is some evidence in favor of *preadult hyperfunction* of the anterior lobe, and quite definite proof that this lobe is *not hypofunctioning* at the present time. The following points are in favor of preadult anterior lobe hyperfunction: (1) the history of very rapid growth before adolescence, so that the present height of 5 feet 10½ inches was reached by the age of 14 years; (2) the hands are the type "en longe"—large but well-proportioned with wide wrist and palm, and long fingers which show some tufting of the distal phalanges; the lunar markings of the nails are well developed; the feet show the same characteristics; (3) large, well-proportioned head; (4) prominent malar bones and mandible, with slight tendency toward prognathism of the latter; (5) well-developed and preserved teeth showing large upper incisors and good spac-

ing; (6) perfect development of the sex organs, with a tendency to over-development of the uterus.

In the introduction to this paper attention was called to the fact that those cases which begin with preadult hyperfunction of the anterior lobe have a remarkable tendency to later pass into the hyposecretory state, involving one or both lobes. In this case there is sufficient evidence to show that the anterior lobe has *not* been involved in the change to hypofunction, for if it had disturbances in menstruation would accompany the change. Repeated questioning on this point shows that the regularity, duration, and amount have remained normal in spite of the marked constitutional symptoms. It is, however, not possible, at the present time, to say whether the anterior lobe is still hyperfunctioning or has returned to a normal state. Observation for a long period of time will settle this point by revealing the presence or absence of beginning acromegaly.

*Posterior Lobe.* The continuous low and unstable blood pressure, headaches, increased carbohydrate tolerance, obstinate atonic constipation which has become worse as the symptoms progressed, weakness, great fatigability, and increased tolerance to pituitrin are all characteristic of hypofunction of this lobe. This diagnosis is further substantiated by the response to treatment and the decreasing tolerance to pituitrin which accompanied improvement.

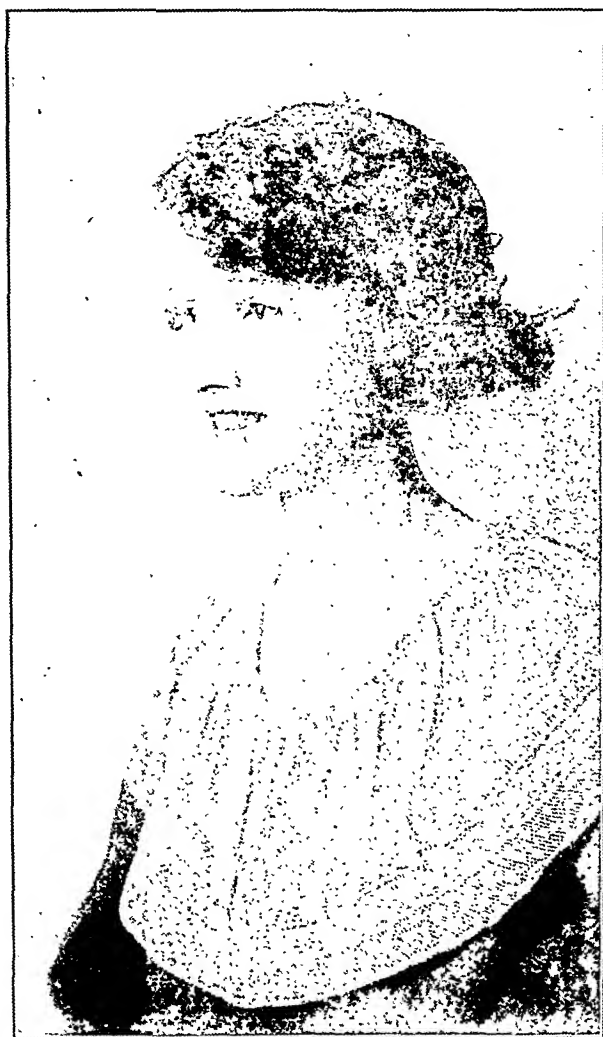
*Hyperthyroidism.* Slight hyperthyroidism has very frequently been found to accompany hypersecretion of the anterior lobe of the pituitary gland (2). The proofs of its existence in this case are *the slight enlargement of the thyroid gland, increased basal metabolism, loss of weight and a positive Goetsch test.* This complicating slight hyperthyroidism has to some extent prevented the full development of the signs due to posterior lobe pituitary hypofunction. Under function of the pars nervosa of the pituitary and hypersecretion of the thyroid have exactly opposite effects on metabolism, fat deposition, carbohydrate tolerance, temperature, pulse, blood pressure and intestinal peristalsis, and when these two conditions are coexisting a balance of function must result. In this case the *increased basal metabolism, and the absence of pituitary obesity* are probably due to hypersecretion of the thyroid, which, however, has not been suf-

ficient to overcome the effects of hypopituitarism on the *carbohydrate tolerance, blood pressure, intestinal peristalsis, and temperature.*



*Diagnosis.* The case was diagnosed as follows: (1) preadult hyper-function of the anterior lobe of the pituitary gland, followed by postadult hypo-function of the posterior lobe, the anterior lobe either remaining hyper- or becoming normal in func-

tion; (2) slight hyperthyroidism; (3) cutaneous hyperalgesia of the abdominal wall due to impingement of cutaneous nerves



These pictures were taken several months after treatment had been started, at a time when the patient was well on the road to recovery.

by the scar; possible postoperative adhesions to the parietal peritoneum.



## 544 HYPERPITUITARISM WITH HYPERTHYROIDISM

## TREATMENT AND PROGRESS

On 7-30-22 the patient was started on the following treatment: 10 grains of pituitary extract (whole gland) by mouth, after each meal and at bedtime, subcutaneous injection of 1 cc. of pituitrin (S) to be given twice per week.

On 8-12-22 she left the hospital apparently feeling better, but the change was so slight and the time so short that no definite conclusions could be drawn. She was instructed to keep on taking the 40 grains of pituitary extract daily and to return to the hospital twice per week for the injections of pituitrin. She was also instructed to get 8 or 9 hours' sleep, to take short daily walks as soon as she was able, to eat regularly and to drink large quantities of milk.

On 9-20-22 the subject weighed 142½ pounds, a gain of 16¼ pounds after 7 weeks of treatment. There has been a gradual amelioration of all symptoms. The headaches have slowly disappeared and she now has been entirely free from them for the last two weeks. She does not have the attacks of vertigo when she arises from a sitting or lying posture, and has not had a fainting spell since she left the hospital. While she was in the hospital it was found necessary to give daily enemas or cathartics to produce bowel movements, but she now states that she has daily spontaneous evacuations without these measures. The appearance is also much improved, the eyes are bright and full of expression, and the dull, worried, haggard look is gone.

## POSTURAL BLOOD PRESSURE CHANGES, SEPT. 20, 1922

<i>Position</i>	<i>Systolic</i>	<i>Diastolic</i>	<i>Pulse Pressure</i>	<i>Pulse Rate</i>
Lying .....	128	82	46	72
	126	80	46	76
	128	84	44	..
Sitting .....	122	84	38	88
	120	86	34	..
Standing .....	118	88	30	120
	118	90	28	..
	120	92	28	..

When the above figures are compared with those obtained 7-24-22 a great improvement is noted, and it is now clear why the fainting and dizzy spells, formerly encountered on change of posture, are no longer present.

On 9-24-22 a second carbohydrate tolerance test was done and a rather marked decrease in tolerance was noted. See Chart 1 for explanation and comparison of the curves.

9-27-22. *Basal Metabolism.* An average of two separate determinations gave *minus 5.8 per cent.* The determinations were well controlled and done under favorable conditions.

GOETSCH TEST, SEPT. 30, 1922

<i>Time</i>	<i>Systolic</i>	<i>Diastolic</i>
Before injection .....	128	80
Three min. after injection of .5 cc. of 1-1000 Adrenaline Cl.....	150	88
6 minutes .....	148	80
9 minutes .....	146	78
12 minutes .....	142	80
15 minutes .....	132	78
18 minutes .....	132	80
21 minutes .....	140	78
24 minutes .....	140	80
27 minutes .....	132	78
30 minutes .....	136	80
1 hour and 10 minutes.....	128	80

Subjective signs and symptoms, such as increased respiration, nervousness, throbbing pulsations in the vessels of the neck, etc., were present but much less marked than on the former occasion. According to the standards set by Goetsch, the test would still have to be considered positive, but when compared with the test done 7-25-22 some marked differences are seen. To begin with, the systolic pressure is now 28 mm. higher than it was formerly. The height reached by the systolic pressure after injection is practically the same—148 mm. formerly and 150 mm. now—but owing to the difference in the systolic pressure before injection, the total rise in pressure is now much less—48 mm. formerly and 22 mm. now. Just how this change is to be interpreted I am unable to say.

## PITUITRIN TEST, SEPT. 30, 1922

<i>Time</i>	<i>Reaction</i>
3 min. after 1 cc. of Pituitrin (S) intramuscularly	Headache, slight abdominal cramps and slight pallor.
25 minutes after.....	The abdominal cramps have been increasing in severity and the patient has just had a bowel movement. Pallor is very marked. Is having severe psychic reactions in the form of crying, etc.
35 minutes after.....	Abdominal cramps still present, but much less severe. Pallor less. Psychic reaction is over.
40 minutes after.....	Reaction over.

The above reaction is positive. Two months ago, when the same test was done, before treatment was started, an entirely negative reaction was obtained, i. e., little or no intestinal cramps and no vascular or psychic reaction. There is therefore a decrease in the tolerance to pituitrin.

On 3-4-23, all treatment was stopped. For about three weeks her condition remained unchanged, but after this she began to develop the same symptom complex that had first brought her to the hospital. None of these symptoms, however, reached the grade of intensity that had prevailed at that time. On 4-24-23, she was again started on whole gland extract, 40 grains by mouth daily, and this was continued until 5-18-23 with a slight amelioration of all symptoms. On this date she was started on 1 cc. of Pituitrin (S) subcutaneously twice per week in addition to the whole gland by mouth. The improvement was now more marked and continued until she was again entirely free of all previous complaints. At the present time, after one and one-half years of observation, there has been no return of symptoms, but the above treatment has been intermittently continued for the greater part of this time.

## DISCUSSION

There is always a certain amount of psychic, subjective improvement apt to occur in these cases shortly after treatment is started; but if this is the only basis for improvement it will usually disappear after a short time and the former symptoms return. In this case sufficient objective and metabolic changes were brought about to eliminate the purely psychic element of amelioration. These changes consist of gain in weight, establishment of a normal and stable blood pressure, reduction in basal metabolism, restoration of sugar tolerance to almost normal, decrease in the tolerance to pituitrin, and the disappearance of an obstinate, atonic constipation.

Increased basal metabolism and loss of weight are contrary to what we should expect to find in hypofunction of the posterior lobe of the pituitary, and are attributed to a complicating slight hyperthyroidism. If this explanation is correct, it seems unreasonable to believe that the basal metabolism would be restored to normal and a gain of weight brought about by pituitary treatment. This amelioration of hyperthyroid symptoms by treatment with pituitary extracts, however, has been noted clinically by other investigators; Richter (3), Pal (4), McGraw (5), and Hofstatter (6) have all reported cases which support this view. Engelbach has observed, in addition to the disappearance of hyperthyroid symptoms, a reduction of basal metabolism as demonstrated in this case.<sup>4</sup> These observations, however, have not been well enough controlled, or sufficiently checked by others to allow definite conclusions to be drawn from them, but, if correct, offer an explanation for the equivocal changes found in this case.

The effect of the anterior lobe of the hypophysis on basal metabolism is unsettled, and I have followed Engelbach in believing that its effect is nil. Aub and Taylor (7), in a recent review of the data on this subject, state: "Work on the pituitary suggests that hypersecretion of the anterior lobe may cause a slight rise in metabolism, although this fact is not yet well established."

Engelbach, Cushing, and the majority of clinicians, believe that the development of pituitary obesity depends on hyposecre-

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4. Personal communication.

tion of the posterior lobe, and I have attributed its absence in this case to two factors; first, the patient was seen and treated early, possibly before the disorder was fully established, so that the obesity may have developed later; second, the effect of the hyperthyroidism may have been sufficient to totally prevent its development. Engelbach (8) finds evidence to believe that if hypofunction has been preceded by hyperfunction of the posterior lobe, then the typical obesity does not develop. There was no evidence, however, of preceding hyperfunction in this case. There is another possible explanation based on experimental data, namely, that hyposecretion of the anterior lobe is the factor which causes the development of pituitary obesity.

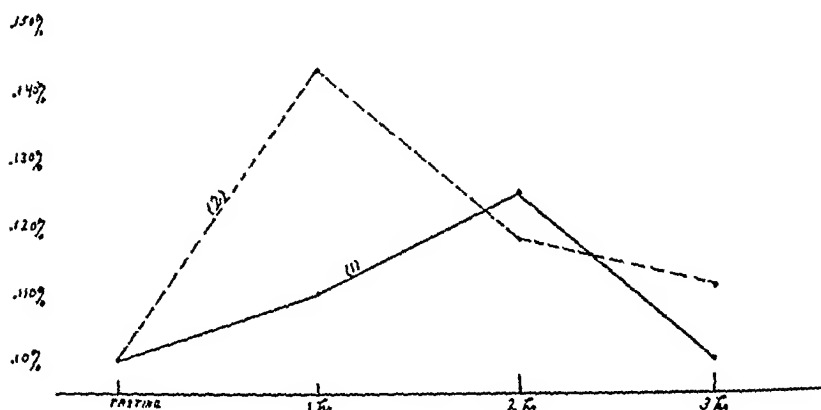


CHART I

CURVE 1 7/29/22

CURVE 2 9/24/22

Pure dextrose, 1.75 grams per kilo, was given in both instances. The first curve is definitely lower than normal. The second curve is a normal type, and the maximum height is only slightly below the minimum height of a normal curve. We consider a normal curve to be one that reaches its maximum height (between 0.15% and 0.18%) in one hour, and returns to normal at the end of three hours. Simultaneous specimens of urine were dextrose free in both tests.

Beck, in *Endocrinology and Metabolism* (9) states, "Experimentalists generally believe that, the adiposity of dystrophia adiposogenitalis is due to hypofunction of the anterior lobe, because removal of the anterior lobe, or posterior lobe plus a large part of the anterior lobe, will give adiposity, while simple removal of the posterior lobe will not." If this is true, then we are mistaken in considering the Lorrain-Levi type of hypopituitarism as due purely to anterior lobe hypofunction, because in this type the typical pituitary obesity is not present (10). The

excellent response of many of these cases to treatment with anterior lobe extracts makes the experimental evidence seem doubtful, and further work in both clinic and laboratory will be necessary to clear up this question.

The relation of hypopituitarism to fainting attacks has been emphasized by Pierce (11). He reports cases in rapidly growing adolescents with fainting attacks, fatigability, low blood pressure, etc., due to hypopituitarism, who are benefited by by treatment with pituitary extract. He makes no attempt to analyze the symptoms from the standpoint of lobar function, but apparently attributes them to hypofunction of the whole gland.

The possibility of spontaneous cure or improvement in these cases, by enlargement and increased function of the pituitary, has been observed by Timme (12). He reports a series characterized by headaches, fatigability, low blood pressure, low blood sugar and vasomotor instability, many of which improved without treatment, and in these cases he was able to demonstrate that erosion and enlargement of the sella turcica had occurred. All of his cases were improved by continuous feeding of pituitary extract. He believes that the syndrome is pluriglandular, involving the thymus, adrenals and pituitary, with hypofunction of the latter as the primary factor.

Cases similar to the one under discussion are by no means uncommon,<sup>5</sup> and it is of great importance to differentiate them from *primary* slight hyperthyroidism in order to avoid needless surgical or other therapeutic measures. If the signs of a pluriglandular syndrome with primary pituitary disturbance are recognized, it may be possible totally or partially to relieve the hyperthyroid and other symptoms by restoring normal pituitary balance.

In conclusion I wish to thank Dr. Albert Taussig, Chief of the Medical Service of the Jewish Hospital, for his interest and permission to publish the case, and Dr. Wm. Engelbach and Dr. C. H. Neilson for their kindness in reading the manuscript and offering many valuable suggestions and additions.

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5. Personal communication from Dr. Engelbach.

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## END RESULT IN THYROTOXICOSIS

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The following case is reported in order to increase the number of case histories in the literature depicting the conditions found at autopsy in cases of thyrotoxicosis treated by operative methods. Up to the present, we have obtained only the reports

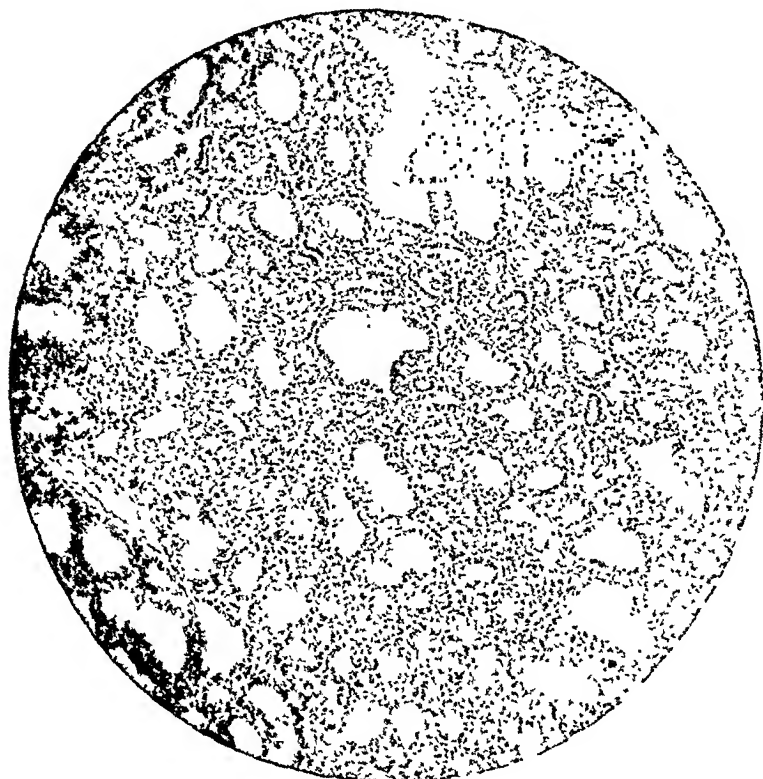


FIGURE 1

as to the immediate operative effects and very few reports showing the ultimate effects and the conditions under which the patient died.



The patient in the following protocol had been operated on twice and had also been treated with the injection of boiling water, and yet died some years later with all the symptoms of acute thyrotoxicosis and evidence of proliferation of the thyroid gland.

George Martin, a white male, aged 50 years, was first admitted to the General Hospital on April 15, 1921. He was a widower; occupation, cook.

The *family history* was negative.

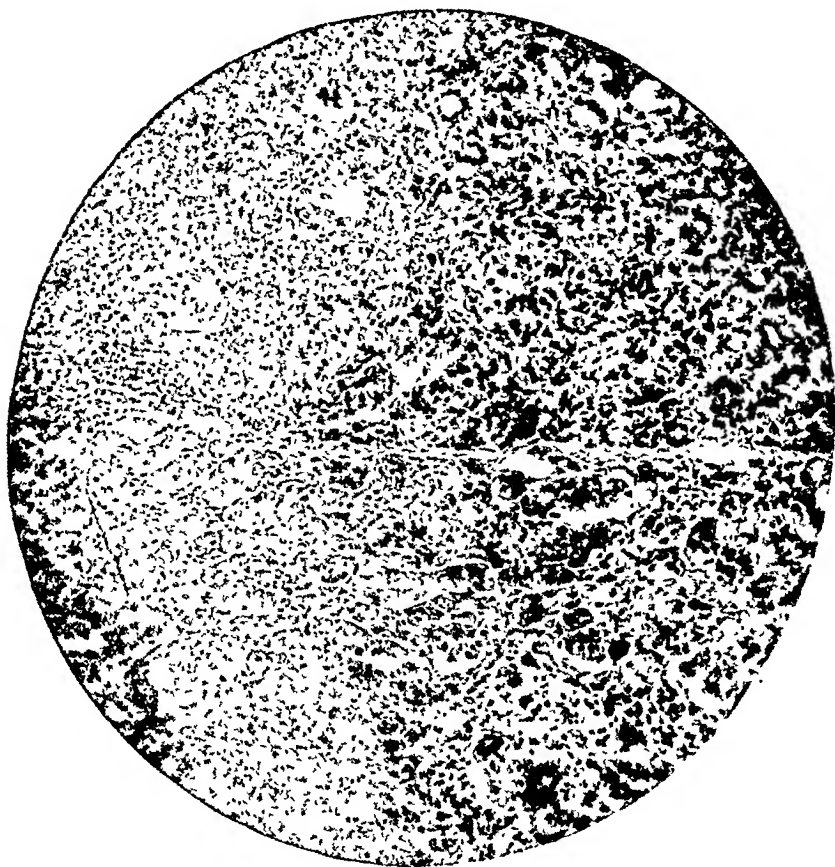


FIGURE 2

*Personal History: Chief Complaints.* The patient complained of (1) swelling of the feet and ankles; (2) weakness; (3) palpitation of the heart; (4) enlargement of the thyroid gland.

The present trouble is apparently an exacerbation of a condition existing from the age of twelve. Enlargement of the gland and bulging eyes were the first symptoms noticed. Other symptoms appeared,

and twelve years ago part of the thyroid gland was removed while the subject was in California. This was followed by a cessation of symptoms, and the patient was able to work until three weeks ago, when the old symptoms reappeared, together with loss of weight (30 pounds in two months), and also an enlargement of the thyroid gland.

*Physical Examination. Positive Findings.* (1) the face and neck are very red and flushed. (2) The eyes are bulging, especially marked in the left. All signs of exophthalmos are present. (3) The thyroid is enlarged, with depression in the region of the isthmus. The en-

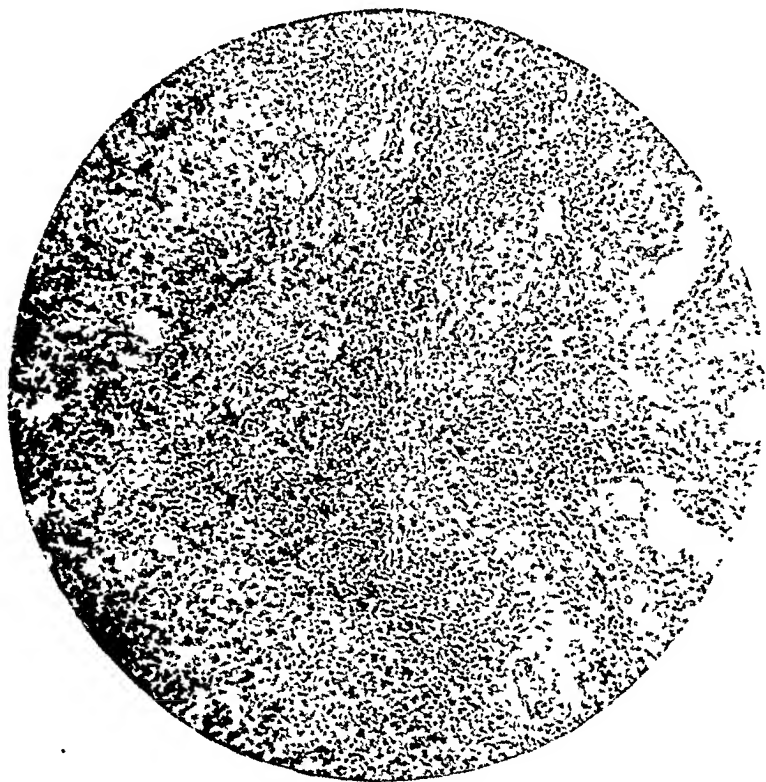


FIGURE 3

largement is bilateral, but is more marked on the left. The gland is firmer on the left. A scar shows the site of the previous goiter operation. (4) The heart sounds are irregular in force and frequency. The second sound is accentuated and sharp. A low-pitched systolic murmur is heard at the apex and base; it is best heard over the aortic area. The heart is enlarged downward and to the left. The heart rate is 80 to 100. (5) There is moderate sclerosis of the radials. Marked pulsations in the neck are observed. The blood pressure is

60 to 160. (6) There is a fine tremor of the tongue and fingers. (7) Co-ordination and mentality are good. (8) Brownish discoloration and healing ulcers are noted on both legs from the middle to the lower third.

*Provisional Diagnosis* was as follows: (1) exophthalmic goiter; (2) myocarditis; (3) dilated aorta; (4) lues, tertiary.

*Laboratory Reports.* (1) Urinalysis on three occasions was negative. (2) The blood count is: Hb., 75 per cent; erythrocytes, 4,200,000; leucocytes, 4,000; differential, p. m. n., 52; small lympho-

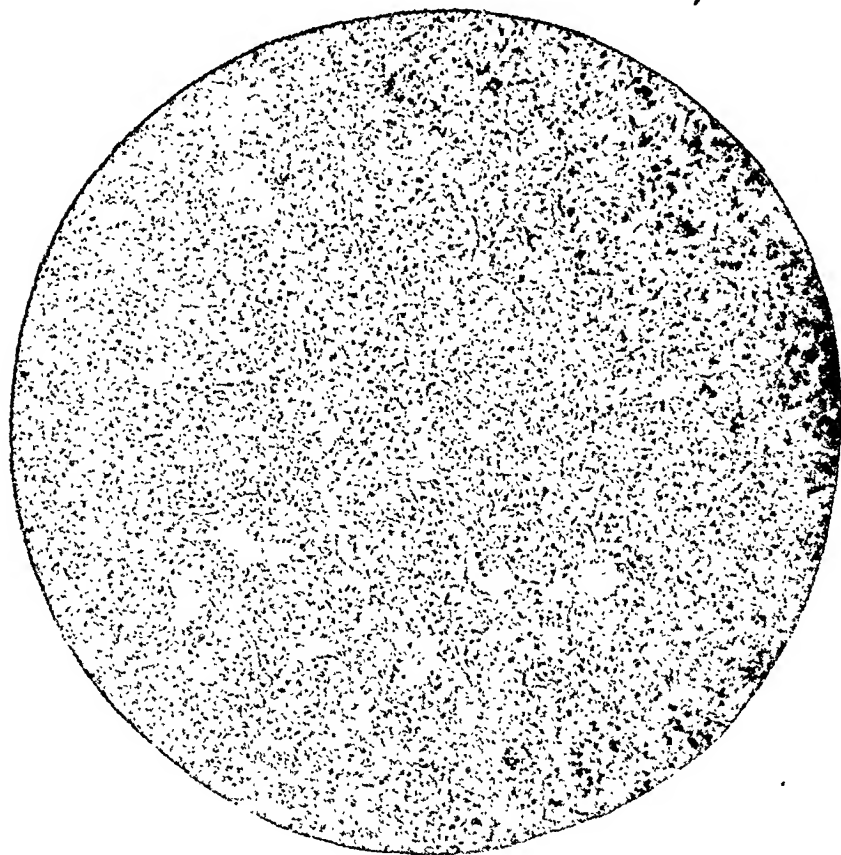


FIGURE 4

cytes, 40; large lymphocytes, 5; large mononuclears, 9; and transitional, 1. (3) The Wassermann determination is 4 plus. (4) X-ray examination, 4-18-21, showed a very large heart with much density about the mediastinum and chronic fibrosis throughout the chest. On 7-6-21 there was density in the upper midline suggestive of an enlarged thymus.

The patient was treated medically by rest in bed, digitalis and antiluetic therapy until the symptoms were alleviated sufficiently for operation, which was done on June 3, 1921.

*Operative Report.* As anesthetics novocain and ether were used. A portion of the left lobe was removed—two by three inches. Bleeding was profuse. The superior thyroid artery was ligated. Microscopic examination of the tissue removed showed extreme hyperplasia throughout. Possibility of malignancy was noted.

On June 24, 1921, under local anesthetic, 2 cc. of boiling water was injected into the right lobe.

The patient was discharged on July 13, 1921, in a much improved condition.

#### SECOND ADMISSION—JAN. 9, 1924

*Chief Complaints.* The subject complained of: (1) a choking sensation; (2) nervousness; (3) a very definite psychosis and status not dependable. He was not oriented as to time or place.

*Physical Examination: Positive Findings.* (1) The face is flushed. (2) The eyes are bulging, the conjunctiva congested. The right pupil is larger than the left; both react to light and accommodation. (3) There is an old scar on the neck. The thyroid is enlarged bilaterally. (4) The heart is enlarged down and to the left. The sounds are fast and irregular. No murmur can be heard. (5) Healed ulcers are seen on the anterior surface of both legs.

*Laboratory Reports.* (1) Urinalysis is negative. (2) Blood counts and smears are normal except for 9 mgs. calcium per 100 cc. blood.

The patient had to be put in the psychopathic ward. He did not respond to medical treatment on account of his constant psychosis and lack of co-operation. He developed pneumonia after two weeks. While febrile his delirium lessened, but during convalescence his motor mania returned. He was sent back to the psychopathic ward. Two days later he developed facial erysipelas and died Feb. 13, 1924.

*Autopsy Report.* The lungs showed broncho-pneumonia in the lower left lobe—of the terminal infection type. The heart showed several sclerotic changes. The aorta showed occasional atheromatous changes. The liver was congested. The kidneys showed an interstitial nephritis of low degree. The thyroid showed hyperplasia with a tendency to infiltration in the spaces about all the surrounding structures. The consistency of this hyperplastic tissue was of a curious uniformly livid type, reminding one of malignant degeneration.

The microscopic slides show proliferation of the glandular elements of the thyroid with a decrease in the colloid. There is considerable round cell infiltration and other evidence of rapid growth. Dr. Hertzler, who saw these slides, classifies the picture as that of thyr-

toxicosis rather than that of exophthalmic goiter. Dr. Trimble, however, favored a diagnosis of beginning malignancy. The accompanying photomicrographs illustrate some of the difficulty of interpreting the nature of the process.

The case shows how little operative treatment gets at the cause of the proliferation of thyroid tissue. The history shows also the effects of an overactive thyroid rather than those of a carcinoma.

# RICKETS AND PARATHYROIDS

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PHILADELPHIA

It is now ten years since Erdheim (1) pointed out the probability of a relation between rickets and parathyroid function. He developed the thesis from the observation that a marked enlargement of the parathyroids frequently occurs during spontaneous rickets. He interpreted this enlargement as the consequence, not the cause, of the rachitis. The correctness of this interpretation will be discussed during the analysis to be given in this paper.

Both rickets (2) and parathyroid deficiency (3) produce retardation of ossification of the bones of young and growing animals. Because of the presence of this common symptom in the two disturbances, there has been a tendency to consider parathyroid deficiency as an etiological factor in the distortion of bone growth in rickets, in the sense that the dietary defect acts to retard ossification through intermediation of the parathyroids. Such a contention is untenable in the light of recent investigations.

Now retardation of ossification occurs when the organism lacks the ability to lay down the essential calcium salts in the bones, or when the essential components of these salts are not available in requisite amounts.

While it is possible that the former type of deficiency participates in rickets and after parathyroidectomy, we have no certain evidence that such is the case. On the other hand, there is evidence available which demonstrates not only a lack of the elements essential for the formation of osseous tissue, but also a disturbance of the phosphorus-calcium ratio which McCollum (4) has shown to be so important in bone formation. It is this deficiency and the disturbance of the ratio which allows a differentiation of the two pathological conditions.

The lack of available bone building materials and the disturbance of the phosphorus-calcium ratio is different in rickets

than in parathyroid deficiency. It is this fact which allows the elimination of the parathyroid factor as a participant in the retardation of ossification in rickets.

Let us first consider rickets. In this disorder there is less phosphorus in the blood than is found in normal persons. On the other hand the calcium content of the blood is essentially within normal limits (5). In other words, the phosphorus-calcium ratio is decreased. Since the formation of bone of normal composition depends upon an adequate supply of both phosphorus and calcium in normal ratio, it is obvious that the decrease in the one element (phosphorus) with the other (calcium) remaining normal—as occurs in rickets—is the immediate important factor in the retardation of ossification in this disease. This belief is substantiated by the fact that the feeding of cod-liver oil to rachitic animals raises the phosphorus content of the blood and with this increase there occurs a release from inhibition of ossification (6).

It is evident, then, that the action of the lack of essential vitamin on ossification is exerted in large part through its effect on the phosphorus side of the phosphorus-calcium ratio.

Turning now to the consideration of the condition of parathyroid deficiency it is seen that a picture of an entirely different type is presented. Here calcium instead of phosphorus is low in the blood, calcium is lost from the body (7) and the phosphorus of the blood tends to be increased (8) and less is excreted in the urine. This is reflected in the composition of the ash of the bones in which a decrease in calcium per cent and an increase in phosphorus per cent obtains (9).

It is evident, then, that the action of parathyroid deficiency on ossification is exerted in large part through its effect on the calcium side of the phosphorus-calcium ratio. An effect which is quite the opposite of that exerted by the vitamin deficiency which produces rickets.

The two mechanisms by which retardation of ossification is produced are thus seen to be distinctly different, although they do produce like end results. This similarity of end result, retardation of ossification, proceeding from opposite types of distortion of the phosphorus-calcium ratio, is understandable when it is realized that an adequate amount of both calcium and

phosphorus in proper ratio is necessary for normal bone substance formation.

Although the foregoing analysis demonstrates that the parathyroids cannot be considered as etiological factors in the production of rickets, there remains the necessity for an explanation of the enlargement of these glands in that disease. Such an explanation is derivable from available data.

A recent study of Grant and Gates (10) showed that radiation of rabbits with ultra-violet light produces an increase in the blood calcium which is accompanied by an increase in the size of the parathyroids. This response parallels Erdheim's (1) observation of parathyroid enlargement in rickets. Correlating these findings with those already given it is evident that a lowering of the phosphorus-calcium ratio causes a disturbance in parathyroid function, probably in the direction of an increased activity. On the other hand, when a parathyroid deficiency exists the opposite reaction is elicited, e. g., an increase in the phosphorus-calcium ratio. Such being the case it is clear that Greenwald's (11) belief that any theory of the causation of tetania parathyreopriva must take into consideration these changes in calcium and phosphorus is well founded. However, it is necessary, I believe, to extend the conception away from circumscribed attention to calcium deficiency as such, such as has occupied workers in this field in the past, and to focus it upon the change in the phosphorus-calcium ratio. On this basis, then, a function of the parathyroids is associated with the maintenance of the phosphorus-calcium ratio, whether directly or indirectly it is impossible to determine at the present time, and a disturbance of this ratio such as occurs in rickets or after radiation with ultra-violet light produces an attempt on the part of these glands to maintain the equilibrium, which attempt is expressed in hypertrophy.

#### SUMMARY

Although the parathyroid glands are probably intimately concerned in the maintenance of the phosphorus-calcium ratio and hence in ossification as shown by their enlargement when this is disturbed and the disturbance of the ratio in conditions of parathyroid deficiency, yet they are not to be considered as



active participants in the retardation of ossification observed in rickets because of the fact that in rickets the disturbance of the phosphorus-calcium ratio is in the direction of a decrease of this value, while in parathyroid deficiency the distortion is the opposite in direction, that is, an increase in the value of the ratio. Such being the case the two conditions are not to be confused even though the end results—retardation of ossification—are similar.

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# Book Reviews

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## THE AUSTRALIAN JOURNAL OF EXPERIMENTAL BIOLOGY AND MEDICAL SCIENCE.

On March 15, 1924, there appeared the first number of a new quarterly journal, The Australian Journal of Experimental Biology and Medical Science. This journal is published at the University of Adelaide for the Medical Sciences Club of South Australia and it is sustained by the Miss A. F. Keith Sheridan Bequest to the University of Adelaide for medical research. The managing editors are Professor J. B. Cleland and Professor T. Brailsford Robertson. These gentlemen will be assisted in the selection of papers by a board of editors consisting of seventeen well-known and prominent members of medical, biological and veterinary circles in different States of the Commonwealth. It is intended to publish articles embodying the results of original research in bacteriology, biological chemistry, experimental medicine or surgery, experimental pathology, experimental zoology, genetics, immunology, parasitology, pharmacology and the physiology of plants and animals. The first number consists of 37 pages and contains four articles. A. B. Anderson reports his observations on the effect of phloridzin on the mortality from "insulin" hypoglycemia in mice. M. T. Mitchell contributes an article entitled "The Substitution of Taurine for Cystine in the Diet of Mice." O. W. Tiegs discusses the mechanism of muscular action and T. Brailsford Robertson writes upon the influence of hydrolysis upon the capacity of proteins to bind acids and bases.—*Med. J. Australia*, 1924, i, 317.

THE ENDOCRINE ORGANS. AN INTRODUCTION TO THE STUDY OF INTERNAL SECRETION. Part I, The thyroid, the parathyroids, and the suprarenal capsules. Sir E. Sharpey-Schafer. Longmans, Green and Co., N. Y., 1924, 2 ed., pp. 175.

The first edition of Sharpey-Schafer's monograph well deserved the popularity which resulted in its soon being out of print. A new edition is correspondingly welcome. It is hoped that the second part will soon be available. The work in general follows the lines of the first edition. The literature has been brought up to date in a thoroughgoing way. A surprising num-

ber of the citations refer to articles published since the war. The bibliography is delightfully free from over-stressing the work of nearby investigators at the expense of that of the geographically remote.

One of the most commendable features in a work of this scope is the placing of the references as footnotes to the discussions. It is presumed that the student who desires an exhaustive treatment of any topic will consult the larger works and utilize their more extensively classified bibliographies.

The illustrations are judiciously selected and the typography is excellent. Altogether the work is to be heartily recommended to those desiring a sane, well-balanced treatise of moderate length.—R. G. H.

FUNZIONI E DISFUNZIONI TIROIDES. L. Castaldi, G. Pighini, U. Cerletti, O. Rossi & E. Lugaro. Instituto Sieroterapico Milanese. 8vo, pp. 288, with illustrations.

This is another series of ten lessons of five studies, a continuation of the preceding volume on "Endocrinologia," instituted by the Instituto Sieroterapico Milanese. This year the theme was limited to the thyroid and related topics. Castaldi emphasizes above all the importance of this gland in body growth; Pighini and Cerletti have investigated two endemic diseases, goiter and cretinism, which, as is well known, are directly related to the thyroid; Rossi illustrates other effects of thyroid dysfunction; and Lugaro points out the relations of this gland to psychical functions.—P. M. N.

LA ACCION FISIOLOGICA DE LOS EXTRACTOS HIPOFISIARIOS. Dr. Bernardo A. Houssay, Talleres Gráficos de A. Flaiban, Buenos Aires, 1922. Pp. 277-340.

This is a continuation of Houssay's exhaustive monograph bearing the same title, issued in 1918. In it the literature is brought up to date and nine pages of bibliography added. The author is to be commended for quoting the references in the original rather than in Spanish translation as in the first installment of the monograph.—R. G. H.

# Abstract Department

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The effect of adrenal substance on the conduct of young white rats. Berman (L.), *Endocrinol. e patol. cositut.* (Roma), 1923, 2, 38-40; abst., *Ber. ü. d. ges. Physiol.* (Berl.), 1924, 23, 114.

Twenty-six day old rats were fed for several days with fresh adrenal substance. Increased liveliness, hyperactivity of the musculature, a quarrelsome disposition and hyperirritability were observed. The young females also showed an aggressive attitude toward animals of the same sex. The investigators concluded that the ingestion of suprarenal cortex influenced the combative instincts and caused a condition approaching suprarenal virilism in females.

—M. D. G.

A quantitative estimate of the catalytic power of adrenaline and thyroxin as calorigenic agents and the relative rate of their destruction. Boothby (W. M.) & Sandiford (I.), *J. Biol. Chem.* (Balt.), 1924, 59, xl.

The administration of both adrenalin and thyroxin produces in the human being an excess of heat over and above that which would have been produced had the substance not been given. It is possible to construct plots integrating this increased heat production for given weights of thyroxin and adrenalin. This has been done and the significance discussed.—F. S. H.

Results of adrenal extirpation (*Über die Ausfallserscheinungen nach Nebennierenextirpation. I. Mitt.*). Bornstein (A.) & Holm (K.), *Ztschr. f. d. ges. exper. Med.* (Berl.), 1923, 37, 1-16; abst., *Ber. ü. d. ges. Physiol.* (Berl.), 1924, 23, 259.

After simultaneous removal of both adrenals in the dog, death followed in 7 to 12 hours. This time was not prolonged by keeping the body temperature constant, bringing the blood sugar up to normal by using pilocarpine or morphine or by extirpating the pancreas at the same time as the suprarenals so that the dog had a high diabetic blood sugar. Constant infusion of adrenalin did not postpone the time of death. Neither did death depend upon temperature fall, drop in blood sugar or deficiency of adrenalin in the blood. The condition was not altered if any of the three mentioned consequences of adrenalectomy were increased. The chief symptom following adrenal removal is increase in respiration. The amount of respired air rises usually twice, often four fold, both the number of respirations and their depth increasing. The alveolar CO<sub>2</sub> tension

decreases greatly, the  $O_2$  consumption is markedly diminished. The increased  $CO_2$  output of the alveoli is quite noticeable in the blood—the  $CO_2$  combining power of which drops from 50-56% to 30-43%. The over-ventilation after adrenal removal is similar in every respect to that of controlled forced respiration in men. In both cases the acidity of the urine sinks together with the ammonia fraction of the total N; true acapnia results in each case. In both forms of over-ventilation death results through paralysis of the respiratory center—the heart continuing to beat. The symptoms of over-ventilation in acute adrenal deficiency seem, therefore, to have a special significance since a large list of other symptoms of over-ventilation can be identified, such as fall in body temperature, lowered blood pressure, rigidity and twitching of the musculature. The source of the stimulus to the respiratory center which leads to over-ventilation is yet to be disclosed. This condition is not prevented by large doses of morphine.—M. D. G.

Treatment of apparent death of the new-born with intra-cardiac injections of adrenalin (*Traitement de la mort apparente du nouveau-né par injection intracardiaque d'adrénaline*). Brindeau (A.), *Bull. soc. d'obst. et de gynéc. (Par.)*, 1923, 12, 467.

Aspiration, and oxygen insufflation having proved inefficacious in bringing to life a new-born infant without cardiac movement, 0.5 cc. of adrenaline was injected into the heart muscle and insufflation was continued. The heart was caused to beat, but the patient died because respiration could not be induced. Meningeal hemorrhage was found at autopsy. Two other subjects reacted similarly.

—F. S. H.

A comparison of the effects of the injection of gum acacia and of the transfusion of blood on the oxidative power of the brain as indicated by alterations in temperature after the injection of adrenalin. Crile (G. W.), Rowland (Amy F.) & Wallace (S. W.), *J. Lab. & Clin. M. (St. Louis)*, 1924, 9, 309-312.

In the bio-physics laboratory of the Cleveland Clinic it has been shown that adrenalin exercises a specific effect on the oxidative powers of the brain, which is manifested by an increased temperature of the brain in direct relation to the amount of adrenalin injected. Employing this as a criterion, it was found that the oxidative power of the brain is markedly diminished by gum acacia solution, while it is increased by transfusion of whole blood.—I. B.

Heat production in the adrenalectomized frog (*La produzione di calore nella rana privata di capsule surrenali*). Gayda (T.), *Gior. d. r. Accad. di med. (Torino)*, 1921, 4s. 27, 403-404.

After the immediate effects of operative trauma have worn off the heat production always diminishes more if the animals have been

completely adrenalectomized. If the adrenals are not completely destroyed the heat production is good until a few days before death.  
—P. M. N.

The human suprarenal cortex in abdominal wounds and in the interesting periods of sex life (*Le cortex surrenal humain dans les plaies de l'abdomen et aux périodes intéressantes de la vie sexuelle*). N. Goormaghtigh, Thesis, University of Grand, 1922.

A detailed description of the cytology and histochemistry of the human suprarenal cortex is given from a normal standpoint. This is followed by a record of observations made on cortical material secured from war victims immediately following death, using cases in which death was due to peritoneal hemorrhage or peritonitis following abdominal wounds. Then follow observations on cortical material obtained at the important periods of sex life secured after death due to accident.

The adult normal cortex of the adrenal is composed of four zones in order from inside to outside as follows:

(a) Juxtamedullary, a thin band composing about one-eighth of the total cortex; it is itself composed of irregular, anastomatic, monocellular cords surrounding the blood capillaries and lymphatics. In man these cells are in immediate contact with the medullary cells. Their secretory activity is manifested by their formation of pigment.

(b) A zone corresponding to the superficial part of the reticularis, composed of parallel columns which are made up of turgescient polyhedral cells with pale and finely granular cytoplasm. The nuclei are spherical and usually contain two nucleoli, but the important morphological characteristic of these cells is that they contain no lipoid in the state of droplets, thus marking the point of the departure of lipogenesis. In the superficial part of this zone is a new cell type, the siderophile cell of Ciaccio: elongated cells located on the surface of the columns and running parallel with them. They are rich in mitochondria and are usually attached to each other forming cell trains extending into the adjacent zona spongiosum. Their secretory activity is manifested by the appearance of small granules that increase in number while the mitochondria diminish as the cells extend into the adjacent zona spongiosum. These cells play an important rôle in lipogenesis, the lipoids being nonlabile.

(c) Zona spongiosum, forming two-thirds of the cortex composed of cells resulting from the progressive transformation of the siderophile. The insensible disappearance of the siderophile is brought about by accumulation of a considerable number of large droplets and the diminishing of mitochondria. These spongiocytes act as lipoid reservoirs and represent the final morphological expression of the lipogenesis. The lipoids are labile.

(d) Zona glomerulosa, a thin layer of cell cords composed

principally of two cell types; a clear pale cell and a dark cell. A few spongiocytes with small droplets may be seen.

The histochemical reactions of the cortical lipoids as regards fat stains and solvents is discussed and systematized.

In peritoneal hemorrhage there is a rapid increase of the labile lipoids in the deeper zones of the cortex (fasciculata and reticularis).

The influence of peritonitis on the cortical lipoids shows that the functional activity is secretory and excretory. Extending over a period of six days there are three excretory and two secretory phases. First there is a discharge of lipoids, then a renewal followed by a second discharge. This in turn is followed by a second renewal and another discharge. During the renewal of lipoids the siderophiles greatly increase in number. The cortex is a regulator of the cholesterine chemistry of the body. The observations show that the outer seven-eighths of the cortex produces an antitoxin (ethers of cholesterine) to aid the organism to combat infection. The inner one-eighth takes no part in this production.

During the important periods of sex life, birth, confinement, menopause, and old age, the juxtamedullary zone shows marked changes in size and activity independent of the other zones, a fact which would indicate that this zone controls manifestations of sex life, especially the secondary sexual characteristics.—E. B. Hanan.

The adrenalin injection test in Basedow's disease (*L'épreuve de l'injection d'adrénaline dans la maladie de Basedow*). Labbé (M.) & Lambru, *Ann. de méd. (Par.)*, 1923, 14, 423-430.

The application of the Goetsch test to 10 healthy subjects produced a slight increase in pulse and respiration rate, no glycosuria, and but little hyperglycemia. Palpitation, tremor, asthenia, sweating or rise in temperature were not observed. Ten patients with Basedow's disease responded to the same test as follows: 70% marked hyperglycemia; 80% greater than normal reaction of pulse; oculo-cardiac reflex inverted in all cases. The test is therefore considered as of moderate value only in the diagnosis of Basedow's disease, since all other manifestations were as in the controls. In sympathicotonia, however, the reactions are striking. An analysis of the reactions of the two disorders to the test is given.—F. S. H.

Adrenalin administered per rectum in children (*L'adrénaline administrée par voie rectale chez l'enfant*). Lesné (E.) & Baruk (H.), *Compt. rend. Soc. de biol. (Par.)*, 1924, 90, 389-392.

Five minutes after the administration of 100 drops of 1-1000 solution of adrenalin by rectum there is a rise of arterial tension both maximum and minimum. The pulse is accelerated and hard. The effects appear in 10 to 12 minutes and progressively diminish.

There is no glycosuria. The same dose administered by mouth has practically no effect.—T. C. B.

The relation of Addison's disease to amyloidosis. McCutcheon (M.), Am. J. M. Sc. (Phila.), 1923, 166, 197-200.

A report of a clinically typical case of Addison's disease associated with widespread amyloidosis, which involved the cortex of both adrenals. The amyloidosis was believed to have resulted from a large hypernephroma. Amyloid disease does not often cause Addison's syndrome. In this case it was believed that the destruction of the adrenal cortex by the amyloid degeneration was sufficiently severe to determine the appearance of Addison's disease.—J. P. S.

Adrenal hemorrhage in infancy. Rabinowitz (M. A.), Am. J. M. Sc. (Phila.), 1923, 166, 513-518.

Report of 2 cases of rapidly fatal hemorrhage into the adrenals in two children 18 and 17 months of age, respectively. The condition was characterized clinically by sudden onset in a previously healthy child, rapidly followed by purpura and collapse. The temperature reached 106 degrees in one case and 107.5 degrees in the other. The chief finding at necropsy was a diffuse infiltration of the adrenals, both cortex and medulla, with bright red blood clot.  
—J. P. S.

Toxicity of cocain as influenced by rate of absorption and presence of adrenalin. Ross (E. L.), J. Lab & Clin. M. (St. Louis), 1923, 8, 656-660.

In a series of experiments on cats it is shown that adrenalin markedly increases the toxicity of cocain.—I. B.

The influence of disturbance on the glycosuric action of subcutaneous adrenalin injections (*Beiträge zur Physiologie der Drüsen*. 59. L. Asher. Ueber den Einfluss der Umstimmung auf die glykosurische Wirkung subkutaner Adrenalininjektion). Tsukamoto (R.), Biochem. Ztschr. (Berl.), 1924, 145, 176-192.

Normal rabbits excrete from 3 to 3.6 gms. of sugar after one injection of adrenalin. The percentage of sugar in the urine varies with the amount of urine. Too young rabbits cannot be used for such experiments. When the animals are fed thyroid preparations and react strongly thereto, an actually lesser glycosuria may be produced, but it comes on much quicker. Other animals respond with an abnormally high glycosuria. The phenomena are explicable on the basis of the double action of the thyroid hormone, e.g., the activation against adrenalin and the lessening of the glycogen store. Removal of blood and replacement by transfusion of Ringer's solution with gelatine produces a delayed reaction to adrenalin.—F.S.H.



**Malformation of the adrenal glands with the clinical picture of Addison's disease.** Wahl (H. R.), *Med. Clin. N. Am. (Phila.)*, 1924, 7, 1357-1364.

The case reported is that of a married woman of 46 whose illness began 19 years ago with what she called an early menopause. Five months before death there were marked weakness, considerable diarrhea and rapid loss of weight. The skin had become "copper spotted," especially in the palms of the hands. Five weeks before death the systolic blood pressure was 60 and the diastolic was 40 to 42. A clinical diagnosis of Addison's disease was made. At autopsy no evidence of tuberculosis was found, and the suprarenals, though unusually small, were otherwise apparently normal. Microscopic examination revealed an almost complete atrophy of the adrenal cortex, the medulla having enlarged and accumulated many embryonic neurocytes which seemed to have lost the power of differentiation to a functioning tissue. The author suggests that since there is a close relationship between the suprarenal cortex and the genital organs, it is quite likely that with the cessation of menstruation there was a corresponding atrophy of the cortex, which, by the time the patient died, had almost entirely disappeared.—I. B.

**Innervation of the thymus, thyroid and parathyroids** (*Die Nerven des Thymus*). Braeucker (W.), *Ztschr. f. Anat. u. Entwicklungs-gesch. (Berl.)*, 1923, 69, 309-327.

Technical description of the nerve supply to the thymus, thyroid and parathyroid glands based on dissection of human fetuses. The author concludes that the nerves to the parathyroids and thyroid arise from both the vagus and cervical sympathetics and possibly slightly from the glossopharyngeus in case of the thyroid. The nerves to the thymus arise from the upper thoracic and cervical sympathetics and the vagus and on their way to the gland become associated with the cardiac nerves, blood vessels to the thymus and occasionally the phrenic nerve. The nerves to all these glands are closely interwoven with the nerves to the heart and great blood vessels.—A. T. R.

**Interrelation of the parathyroids, suprarenals and pancreas.** Clark (G. A.), *J. Physiol. (Lond.)*, 1924, 58, 294-301.

The injection of guanidin into rabbits "produces two effects, the first and more powerful being a stimulation of the sympathetic system causing a hyperglycemia, which is probably augmented by an increased production of adrenalin, and the second a hypoglycemia which can be explained by an increased liberation of insulin due to vagal stimulation."—T. C. B.

**Differentiation of human phosphatases** (*Differenzierung menschlicher Phosphatasen*). Forrai (E.), *Biochem. Ztschr. (Berl.)*, 1924, 145, 54-56.

The ability of testes, adrenals, thyroid, pancreas and spleen to split various types of phosphoric acid esters was studied. Other organs were included.—F. S. H.

The occurrence of a hypoglycemia-producing substance in bacteria. Little (J. T.), Levine (V. E.) & Best (C. H.), J. Biol. Chem. (Balt.), 1924, 59, xxxvii-xxxviii.

Bacteria grown in culture media free from substances that may contain insulin, such as peptone, meat, blood, etc., produce a substance which can be extracted by suitable measures and produces hypoglycemia in the rabbit.—F. S. H.

A case of infantilism (Sopra un caso di infantilismo). Pescatori (G.), Gior. di clin. med. (Parma), 1923, 4, 453-461.

A typical case of infantilism of Brissaud's type is described. The mental underdevelopment was scarcely noticeable in comparison with the marked lack of bodily growth. The author believes this condition to be of pluriglandular origin, caused by hypofunction of the thyroid (predominating), hypophysis, adrenals and gonads.  
—P. M. N.

Influence of starvation on the growth and general physical development of children together with anatomical changes during inanition [Der Einfluss des Hungerns auf das Wachstum und die gesamte physische Entwicklung der Kinder (im Zusammenhang mit anatomischen Veränderungen beim Hungern)]. Stefko (W. H.), Ztschr. f. Konstit. (Berl.), 1923, 9, 312-355.

Numerous tables and curves are produced as a result of a study of 800 children belonging to four different races. The author concludes that starvation causes marked growth changes in children at all ages, though all races are not influenced alike. The male is less stable than the female. These growth changes are in a great measure ascribed to effects on the incretory glands, since they undergo changes indicating pluriglandular insufficiency.—A. T. R.

Fructosediphosphatase in human organs (Fructosediphosphatase in menschlichen Organen. I.). Forrai (E.), Biochem. Ztschr. (Berl.), 1924, 145, 47-53.

The presence of an enzyme capable of splitting fructosediphosphoric acid ester was found in the testes, adrenals, thyroid and spleen. Other organs of the body showed the same property.  
—F. S. H.

Opothrapy by radiation (L'opothérapie par les radiations). Schmitt (C.), Bull. gén. de thérap. (Par.), 1923, 174, 538-542.

Stimulative radiation of the thymus in a rachitic infant of 6 months was followed by improvement (doses of 3 minutes each at

intervals of 1 month). Three subjects with amenorrhea treated by monthly radiation of 5 minutes' duration over each ovary were brought to menstruation after a delay of from 8 days to 3 months. Precocious menopause (36-38-39-42 and 43 years) was similarly treated. Menstruation was regulated or reappeared and the nervous disturbances disappeared.—F. S. H.

**Headache.** Tierney (J. L.), *Med. Clin. N. Am. (Phila.)*, 1924, 7, 1515-1544.

Attacks of headache in women are most frequently associated with the menses, and are apt to cease during pregnancy, or with the menopause. Polyuria and bradycardia may occur with attacks of headache. Periodic temporary swelling associated with functional overactivity of the pituitary may explain attacks of migraine better than any other hypothesis. This view, however, seems paradoxical since during pregnancy there is freedom from attacks, although there is an associated pituitary hyperfunction. Moreover, the phenomena of migraine are commonly absent during the course of pituitary tumor. Migraine, with its vasomotor phenomena, is probably due to disturbed endocrine function, in which not only the pituitary, but probably the thyroid and ovaries are involved. Though the pituitary through its vegetative, nervous and vasomotor influence may play a rôle in the production of migraine, the latter must be differentiated from so-called pituitary headache which is a distinct entity. In the author's experience true migraine has been paroxysmal, usually hemicranial, constitutional, hereditary and ordinarily associated with visual disturbance, nausea and vomiting; cases of pituitary headache have commonly been found in individuals with other signs of pituitary disturbance, have been bilateral, non-paroxysmal, associated with different ocular manifestations, if any, and not usually accompanied by nausea and vomiting.—I. B.

**Weight of ovaries with reference to other glands of internal secretion (thyroid, thymus, adrenals) and the uterus** (*Systematische Gewichtsuntersuchungen an Ovarien mit Berücksichtigung anderer Drüsen mit innerer Sekretion, sowie über ihre Beziehungen zum Uterus*). Wehefritz (E.), *Ztschr. f. Konstit. (Berl.)*, 1923, 9, 161-171.

The study involves 730 ovaries, 655 uteri, 529 thyroids, 301 thymi and 701 adrenals from birth to 90 years of age. There were 45 cases of pregnancy from 19 to 46 years of age. The data are tabulated under eleven age groups. The ovaries, thyroid and adrenals during pregnancy average distinctly higher than in the non-pregnant, the ovaries and thyroid being more than 50% larger.—A. T. R.

**Some phases of rejuvenation.** Belfield (W. T.), *J. Am. M. Ass. (Chicago)*, 1924, 82, 1237-1242.

The rôle played by the gonads and the chromatin threads and chromosomes of the cell nucleus of sperm and ovum in the determination of sex is reviewed. Belfield states that in the number of chromosomes of the united sperm and ovum we recognize, not the immutable determination of the sex of the new being, but rather a distinct impulse toward the building of one or the other sex; an impulse that must seemingly be transmitted, as is the distinctive chromosomal structure, to every cell in the body; an impulse which early becomes manifest through the instrumentality of the endocrine glands, including the gonads. This recognition of the fertilized egg as the fundamental factor in sex is essential; it elucidates the otherwise puzzling fact that there is no group of sex features exclusively associated with testis or ovary; and other facts—including possibly homosexuality—inexplicable on the prevalent assumption that sex features emanate from gonads. Defective plans are sometimes manifest in structures deviating from the human type that cannot be explained by human embryology, but which are clearly features of earlier animals in the vertebrate phylum—the so-called arrests of phylogenetic development. The demonstrated difference in cell structure between male and female suggests the possibility that every cell in the body may contribute toward maleness or femaleness; as yet, however, only endocrine glands, including gonads, and cranial ganglions have been proved to make and unmake sex characters. Brown's work indicates that the function of the gonads requires integrity of certain ganglions at the base of the brain, which may be compressed through tumor formation of the pituitary; and that atrophy of the testes may be due to pressure on them rather than to pituitary disease. Among the organs which influence structure and function of the testes must be included certain ganglions at the base of the brain. On the traditional conception that sex emanates from testis or ovary is based the idea that the two sex complexes are essentially antagonistic and immutable. The biologic conception of sex is, on the contrary, not that it comprises two antagonistic entities, but rather that it is a single entity presenting various—and variable—degrees of femininity. There are known many instances in which the female—bird, quadruped or human—has matured normally, and later has assumed in marked degree the features and functions of the male; there is no instance known in which a mature male vertebrate has through intrinsic forces exhibited the corresponding change toward the female type; once a male, always a male; once a female, later a near-male, seems the natural course. Transmutation of females toward maleness, apparently anomalous, is such only in degree; for in all warm-blooded species the heavy burden of reproduction imposed on the female is transitory; and cessation of ovulation is often accompanied by some exchange of feminine for masculine features. Despite the

wealth of pertinent observations, clinical and experimental, the influence of gonads on sex characters is not yet exactly defined.

Homotransplantation of the human testis should, on biologic data, be more promising than that of the ovary; for these data indicate that the somatic tissues, inherited through the fertilized egg from the entire vertebrate phylum, are in harmony with the ancient maleness, but not with the new femaleness of the placental animals—that they are homologous with the testis but heterologous toward the ovary. And since, for the structure and maintenance of sex characters, somatic tissues—the endocrine organs, at least—are as essential as are the gonads, the male castrated before maturity may develop partial maleness, thanks to his somatic tissues, while the spayed young female lapses, thanks to those tissues, from femaleness toward maleness. Hence it seems possible, *a priori*, that a testis transplanted into an otherwise normal young man deprived of the testes might reinforce the maleness of the host's somatic tissues, even though the ovarian transplant into the female fails to do so. Belfield asserts that Steinach's method of rejuvenation merits little attention, for it is founded on error and refuted by experience. Steinach's theory of rejuvenation, for men at least, falls to the ground. The experimental work of careful investigators on rejuvenation by testis implantation seems to have established these results on animals: Testis transplantation succeeds often in young, rarely in old, animals; success meaning merely the maintenance of vitality for a period of months. Though the transplant never produces sperms in its new host, it may function to the extent of preserving the masculinity of a castrated young male for a limited time, or of causing in a spayed young female hypertrophy of the clitoris and distinctly masculine behavior. The life of the transplant is much shorter than that of the native testis; within a few months its elements are replaced by connective tissue, and its physiologic effect on its host ceases. Stimulation of erection sometimes follows testis transplantation in old men, appearing within a few hours and ceasing within a few days. This is apparently the effect of pre-formed substances contained in the transplant and absorbed therefrom by the host's tissues. Similar effects have followed the injection of milk. A lasting recovery of lost erectile power in old men through testis transplantation is yet to be demonstrated. The future of testis therapy seems to depend on the isolation of the activating substance produced in the testis corresponding to thyroxin or insulin. Until this shall be accomplished, the injection of an emulsion of testis tissue seems the most promising form, though such a mixture of unknown proteins must be a tentative remedy. It seems probable that gonad therapy, begun as an irrational attempt at an impossible "rejuvenation," may emerge from the disrepute of its infancy and develop into a valuable means for relieving ailments that are not now associated with gonad deficiency; for it is demonstrated that the gonad does

not originate sex; that it is less essential to the maintenance of sex than is the thyroid or the suprarenal; and that it is indeed one of a chain of interacting endocrine glands, efficiency in every link of which is essential to normal function, sexual or somatic.—Courtesy Am. M. Ass.

**Action of x-rays on the testicle of the cock** (*Action des rayons X sur le testicule du coq*). Benoit (J.), *Compt. rend. Soc. de biol. (Par.)*, 1924, 90, 802-805.

The total disappearance of the seminal cells under the influence of x-rays does not prevent the development of the comb. This sexual character is developed under the influence of the testicular hormone.

—T. C. B.

**Menstruation and lactation. A clinical statistical study** (*Menstruations et allaitement. Observations cliniques-statistiques*). Canelli (A. F.), *Nourrisson (Par.)*, 1924, 12, 92-100.

Twenty-five per cent of the nursing mothers menstruated during lactation. The mean duration of lactation before menstruation reappeared was 4 months and a half. Precocity in this was exhibited in the primiparas. In 90% of the cases the duration of each period was the same as that before pregnancy. In 30% of the cases the periods occurred in regular sequence. Thirty per cent of the nurslings of the menstruating mothers lost weight during the periods, and 17% showed diarrhea.—F. S. H.

**Vaginal rhythm in the hedgehog; effect of injecting follicular liquid** (*Le rythme vaginal du hérisson; action de l'injection de liquide folliculaire*). Courrier (R.), *Compt. rend. Soc. de biol. (Par.)*, 1924, 90, 808-809.

Injection of follicular liquid into a hibernating hedgehog provokes vaginal modifications characteristic of sexual activity.

—T. C. B.

**Relation between the corpus luteum and menstruation** (*Sur les rapports du corps jaune et de la menstruation*). Cotte (G.), *Gynéc. et Obst. (Par.)*, 1923, 8, 517-527.

Report of a series of observations on the histological character of ovaries removed from women at different periods of the menstrual cycle. The results lead the author to believe that the corpus luteum does not play a preponderant rôle in the initiation of the menses, and that if a secretory factor is at work, it probably takes its origin from the different ovarian elements. Moreover, it frequently happened that shortly after the removal of an ovary with a ripe follicle menstruation appeared. An inhibitory effect of the structure is implied by these results.—F. S. H.

The endocrine gland of the deferential ampulla in the horse, ass and mule (*La glandola endocrina dell' ampolla deferenziale degli equidi*). Cutore (G.), Arch. ital. di anat. e di embriol. (Firenze), 1922, 19, 79-94.

There is an interstitial gland in the deferential ampulla of these domestic animals, but it is more developed in the mule than in the horse and ass. Probably this has a slight effect on the secondary sexual characters.—P. M. N.

Preparation and properties of an ovarian hormone. Doisy (E. A.), Allen (E.), Ralls (J. O.) & Johnston (C. S.), J. Biol. Chem. Balt., 1924, 59, xliii-xliv.

A hormone which causes typical estrus in spayed rats has been prepared from liquor folliculi and whole ovaries. The method is given briefly. The hormone is not cholesterol. It is soluble in lipid solvents but insoluble in water. It is stable towards dilute boiling acids and alkali. Dissolved in oil its activity is not destroyed by autoclaving at 15 pounds for 15 minutes. Preparations from placenta, liquor folliculi, and ovaries from which the liquor folliculi have been removed are active; those from embryos and corpora lutea, negative.—F. S. H.

Physiology of Bidder's organ and experimental-physiological sex reversal of male toads to females (*Untersuchungen über das Biddersche Organ der männlichen und weiblichen Kröten. II. Mitteilung: Die Physiologie des Bidderschen Organs und die experimentell-physiologische Umdifferenzierung von Männchen in Weibchen*). Harms (W.), Ztschr. f. Anat. u. Entwicklungsgesch. (Berl.), 1923, 69, 598-629.

The protocol is given of 49 extirpation experiments involving the testis and ovary with and without Bidder's organ. Harms concludes that Bidder's organ of the adult male toad represents a rudimentary ovary-like gonad, with oocytes which mature only as far as the synaptic stage when they degenerate. Or this structure may be viewed as a primitive gonad of the urodele stage of the toad. If the testes of adult toads are removed, the secondary sex characteristics are retained, due to the influence of a male incretion from Bidder's organ. With removal of the inhibitory influence of the testis and over-feeding with fatty foods and lecithin, there is hypertrophy of some of the cells in Bidder's organ till they apparently become normal egg cells. To the extent that this organ changes to an ovary the latent female characteristics develop, i. e., uterine tube and uterus develop and the physical features and behavior become feminine while the male characteristics diminish. Possibly metabolism thus plays an important rôle in the normal differentiation of the sexes in amphibia. Some literature is cited.—A. T. R.

Basal metabolism in insufficiency of the testes, with or without feminism (*Le métabolisme basal dans l'insuffisance testiculaire avec ou sans féminisme*). Harvier (P.) & Van Bogaërt (L.), *Compt. rend. Soc. de biol. (Par.)*, 1924, 90, 672-673.

The basal metabolism is diminished in testicular insufficiency, but approaches the normal when the genital atrophy is accompanied by heterosexual morphology.—T. C. B.

Corpus luteum of the salamander [*Das Corpus luteum des Molches (Triton vulgaris)*]. Hett (J.), *Ztschr. f. Anat. u. Entwicklungsgesch. (Berl.)*, 1923, 68, 243-271.

Description of the changes in the ruptured follicular wall and the formation of a rudimentary corpus luteum, which is similar to the corpus luteum of the fowl.—A. T. R.

Bidder's organ in the frog (*Das Biddersche Organ von Bufo vulg. Laur.*). Hoepke (H.), *Ztschr. f. Anat. u. Entwicklungsgesch. (Berl.)*, 1923, 68, 491-513.

Hoepke concludes from extirpation experiments that Bidder's organ produces an incretion which is useful in the metabolism of the entire body and which cannot in general be dispensed with without damage; but it has no specific action on the secondary sex characters. Some literature is cited.—A. T. R.

Sterility: A study based on a series of 526 patients. Hunner (G. L.) & Wharton (L. R.), *South. M. J. (Birmingham)*, 1924, 17, 269-275.

The authors state that our knowledge of the endocrine aspects of this subject is very meager and they condemn strongly the present tendency to use polyglandular therapy in combating it.—J. C. D.

Case of precocious puberty. Hutchison (R.), *Proc. Roy. Soc. Med. (Lond.)*, 1924, 17, 8-9 (Sect. Dis. Child.).

The case is reported of a girl aged 3½ years who began to menstruate at 17 months and continued at more or less regular intervals of one month up to the present time. The child's weight is 52 pounds, height 44 inches, and the secondary sexual characteristics are well developed. Though dentition is normal, the skeletal development is that of a child of 13 or 14 years of age. Aside from fits of bad temper, the child is mentally normal and bright for her age. The condition is believed to be due to ovarian hypersecretion.—I. B.

Interstitial tissue of the testis of domestic mammals (*Das Hodenzwischengewebe der Haussäugetiere*). Lenninger (W.), *Ztschr. f. Anat. u. Entwicklungsgesch. (Berl.)*, 1923, 68, 230-242.



From an examination of the testes of the horse, cattle, sheep, goat, pig, dog, cat, deer and chamois, Lenninger concluded that the size and number of interstitial cells is not proportional to the prominence of the secondary sex characters. In the deer they increase before and during rut, while after rutting there is an increase in connective tissue. Albuminous crystals could be demonstrated in the intertubular tissue only in the deer preceding rutting.—A. T. R.

The effect of corpus luteum on behavior of rats. Macht (D. I.) & Seago (Dorothy W.), *Proc. Soc. Exper. Biol. & Med. (N. Y.)*, 1924, **21**, 255.

Female white rats tested in a maze responded by an increase in muscular and cerebro-spinal efficiency to injections of corpus luteum and whole ovary. Spayed animals reacted as did normal rats. The effects appeared 15 minutes after injection and lasted 24 hours.—J. C. D.

The scrotum as a temperature regulator for the testes. Moore (C. R.) & Quick (W. J.), *Am. J. Physiol. (Balt.)*, 1924, **68**, 70-79.

In the rat at a room temperature of 14° C. there may be a difference of 7.5° C. between the peritoneal cavity and the scrotum. Evidence is given that the scrotum is a thermo-regulator for the testes.—T. C. B.

Changes in the follicular wall after its rupture in the ovary of the domestic hen (*Die Veränderungen der Follikelhüllen beim Haushuhn nach dem Follikelsprung*). Novak (J.) & Duschak (F.), *Ztschr. f. Anat. u. Entwicklungsgesch. (Berl.)*, 1923, **69**, 483-492.

A description of the formation of a rudimentary corpus luteum from follicular epithelium and theca interna and then its degeneration similar to that which occurs in mammals.—A. T. R.

Racial modifications by ovarian grafts in the cock (*Modifications raciales par greffe ovarienne chez les coqs*). Pézard (A.), Sand (K.) & Caridoit (F.), *Compt. rend. Soc. de biol. (Par.)*, 1924, **90**, 623-625.

In two cases the transplantation into the cock, castrated or not, of an ovary of a hen of a different race provoked a sexual inversion of plumage and the appearance of new pigmentary characters.

—T. C. B.

Cerebral obesity and genital atrophy. Raab (W.), *Wien. Arch. f. inn. Med.*, 1924, **7**, 443-531.

Raab observed 43 patients with cephalic obesity or hypogenitalism. He prefers this term to dystrophia adiposogenitalis because he believes, with Biedl, that the symptoms may be caused either by an

affection of the pituitary gland, or of the brain centers, or of the communication between them. The height of the dorsum sellae in some patients might speak for the latter possibility. In one case the pituitary gland seemed to be the only organ affected. Dystrophia adiposogenitalis is not a uniform syndrome. Each of its component elements may occur isolated. It seems that the centers for the genital organs are on the floor of the third ventricle, nearer to the pituitary gland, while the obesity depends on centers in the tuber cinereum near the mammillary bodies.—J. Am. M. Ass., 82, 1486.

Transplantation of testes from the chimpanzee (*Structure des testicules d'un chimpanzé et résultats physiologiques de leur greffe*). Retterer (E.) & Voronoff (S.), J. d'urol. (Par.), 1923, 15, 417-430; abst., Ber. ü. d. ges. Physiol. (Berl.), 1924, 22, 192.

The testes of a healthy 5 or 6 year old chimpanzee were grafted into two men. The left testis was implanted in a man 52 years old who was in a generally run-down condition, with loss of memory, obesity and impotence. After 3 months the patient had lost 7 kilograms and strength and memory had improved. At the present time, 7 months after the operation, this man gives an amazing impression of youth and strength. The genital function has been completely restored. The right testis of the chimpanzee was engrafted in the other patient 6 months later and up to this time there have been no definite results.—M. D. G.

Hermaphroditismus verus in the human being (*Ein Fall von Hermaphroditismus verus beim Menschen*). Schauerte (O.), Ztschr. f. Konstit. (Berl.), 1923, 9, 373-384.

A 16-year-old twin girl is described who had a fair-sized penis that showed erectile power at the age of 10, a scrotum on one side but also a vulva into which opened the urinary passage. She had many boyish traits during childhood. The breasts enlarged at 14 years and menstruation commenced when 15½ years and remained regular. Laparotomy revealed a normal uterus, one enlarged ovary containing a blood cyst and a normal uterine tube. Section of the scrotal contents proved them to contain a true testis with spermatogenesis going on as far as spermatids. Between the tubules was an abundance of interstitial cells. By the side of each testis was a functioning ovary with ovarian follicles, ova and corpora lutea. Section of the amputated penis showed well-developed corpora cavernosa. After removal of the ovotestis, menstruation continued and the sex inclination of the patient reversed to the feminine side.

—A. T. R.

Testes transplantation. Sechi (E.), Riv. di biol., 1923, 5, 329-346; abst., Ber. ü. d. ges. Physiol. (Berl.), 1924, 23, 114.

after some months. It is apparent that this phase of metabolism is in some way related to the spermatogenous elements of the testicles. The lowered gas metabolism is raised somewhat by implantation of the gonads. Feeding testicular substance had no effect. Thyroid feeding stimulates gas exchange in castrated as well as in normal animals.—F. S. H.

The histologic and physiologic investigation of the so-called phenomenon of rejuvenation (*Beitrag zur histologisch-physiologischen Erforschung der sogenannten Erscheinungen der Verjüngung*. 2. vorl. Mitt.). Wilhelm (O.), *Rev. med. de Chile* (Sant. de Chile), 1923, 51, no. 7-8; *abst., Ber. ü. d. ges. Physiol. (Berl.)*, 1924, 23, 261.

Additional communication on an experiment which has previously been reported. A number of new experiments were carried out on dogs. In an 18-year-old dog there was restoration of the sexual function and remarkable improvement in general condition with unusual increase in weight after unilateral ligation and resection of the epididymis. About 10 months after the operation there was a loss of weight—as much as had been gained immediately following the operation. The sexual power, however, was retained for some time. Some months later a stubborn itch developed; death occurred 1½ years after the operation. The case of an 11-year-old bulldog with unilateral resection of the epididymis is described in detail. The potency was increased, reaching a maximum 6 months after the operation. Then rapid decline took place. Other dogs with unilateral or bilateral ligation and resection of the epididymis were observed. In 4 dogs there were pronounced positive results, bodily as well as psycho-sexual. One animal, in which an epithelioma was also removed, died suddenly 2 months after the operation. A second dog was killed 5 months after the operation for the purpose of histological investigation. The weight had increased from 34 to 44 kg.; complete psycho-sexual regeneration had taken place; there was return of sexual potency and a change in the general condition occurred a short time after the operation. Four months after operation in a third dog there was increase in weight from 16 to 21 kg., rejuvenation of the skin, reduction of the arcus senilis, and extensive changes in the psycho-sexual state. A fourth animal was observed 4 months after operation. There was increase in weight from 18 to 30 kg., complete rejuvenation of the hair and marked change in the general condition. The observations on the third and fourth animals were continued. In a fifth dog the results were negative. It is worthy of note that the operation disclosed an inflammatory change in the subcutaneous tissue and adhesions over the entire extent of the tunica vaginalis and albuginea. In 3 cases of homotransplantation in old dogs (subcutaneous, intramuscular, and intratesticular) the following results were obtained: (1) Sub-

cutaneous transplantation brought about positive results; after subsidence of the positive results, 2 years later, a second transplantation (intratesticular) was performed, but the results were negative. (2) Intramuscular and intratesticular transplantation was performed. The weight increased from 6 to 11½ kg. (The animal was well fed for one month before the operation and the increase in weight was sudden.) Return of sexual potency was noted; he became very aggressive. There was partial rejuvenation of the skin. The animal was in excellent general condition. There was partial disappearance of the arcus senilis. Three and a half months after the operation a decline set in. (3) Intramuscular transplantation was performed. Two and a half months after the operation the dog died suddenly, although potency had returned and the animal seemed more active. There are no definite data concerning the condition of the transplant; gradual resorption probably took place. Further data are reported regarding a previously mentioned patient, operated upon at the age of 62 years (unilateral ligation and resection of the head of the epididymis). There was an extraordinary recovery from angina pectoris; the attacks ceased entirely. A year later there was a return of the phenomenon, successfully treated, however, with testicular extract. In another patient, operated upon at the same time for hernia, there was return of potency and decided improvement in the general condition. The paper includes many splendid photographs of the experimental dogs.—M. D. G.

The induction of labor by quinine and pituitrin. Browne (F. J.), Edinb. M. J., 1924, 31, 25-33.

The author considers that the particular value of this method lies in avoiding the danger of infection, which accompanies the induction of labor by mechanical means.—J. C. D.

A child with congenital syphilis and diabetes insipidus presenting the syndrome of corpora striata lesion. Dwyer (H. L.), Med. Clin. N. Am. (Phila.), 1924, 7, 1201-1204.

The patient is a girl of 8 who came to the hospital 8 months before, complaining of intense thirst and polyuria. After admission, her clinical picture entirely changed, presenting motor disturbances, general muscular rigidity, mask-like facial expression, and tremor. Following antisyphilitic medication the symptoms of diabetes insipidus improved, but the nervous symptoms became intensified.—I. B.

Pituitary tumor. Engelbach (W.), Med. Clin. N. Am. (Phila.), 1924, 7, 1365-1400.

In a series of 375 uncomplicated pituitary disorders, tumor was the cause in only 13 cases. The re-analysis of these cases, some of which have been under personal observance for from 1-10 years,

presented many points incongruous with the present-day teaching. The general hormonal signs are very much more dependable for the diagnosis of secretory disturbances of the hypophysis than the neighborhood and general intracranial symptoms. In one of the 13 cases there was a marked response to specific treatment following simple temporal decompression operation, the patient regaining complete normal vision after having had for a number of months homonymous hemianopsia and incipient optic atrophy. Another luetic case had as its chief complaint glycosuria, which responded temporarily to anti-luetic treatment. In 3 of these cases having a luetic etiology there was absence of an abnormally enlarged sella.

The symptomatology can be readily subdivided into: (I) those symptoms produced by intracranial pressure, and (II) those due to the effect of the hormones of the hypophysis upon other structures and distant organs of the body. (I) The intracranial pressure symptoms can again be subdivided into: (1) neighborhood or localized signs, due to pressure upon the tissues in the region of the pituitary gland, and (2) general intracranial pressure symptoms resulting from increased pressure within the cranium. (II) The hormonal signs are grouped into: (1) general hormonal signs, affecting the individual as a whole, such as height, weight, proportions, adiposity, pigmentations, hair, growth, etc.; (2) regional hormonal signs, which are the changes in local or limited portions of the body, as of the nose, lips, teeth, mammae, genitalia, fingers, toes, etc.; and (3) laboratory signs, which are really a part of the general hormonal signs, but are classed under a different heading on account of the special technic required for their identification. These laboratory signs consist of changes in the basal metabolism and blood chemistry and the effects of the injection of various pituitary substance upon the blood pressure, pulse rate, color, involuntary muscle contractions, urinary output, etc. Pituitary tumors can and occasionally do exist without modifying the size and shape of the sella. In 4 of 13 cases there was no definite enlargement of the sella turcica, and in 3 there was absolutely no enlargement or erosion of any part of the sella portrayed by the radiogram. In some of the others a normal sella for a considerable length of time was demonstrated. Sooner or later, in the majority, erosion of either of the processes or enlargement of the sella occurred. The next most abused neighborhood signs with regard to importance in the diagnosis of pituitary tumor are the ocular signs. A transient, fleeting blindness, asymmetric and varying in its location, is the more constant ocular sign of these tumors. This retinal blindness is due to direct or dragging pressure upon the chiasm or the optic tract just posterior to the chiasm. The amount of retina involved depends upon the location of the pressure, and, in consequence, upon the direction of the growth of the tumor. The amount of blindness may be very small, or may involve the complete half of the eye, or the entire optic tract

may be involved with homonymous hemianopsia, with nasal blindness in one eye and temporal blindness in the other. As the tumor grows, it sometimes decompresses the anterior wall of the sella (the posterior wall of the sphenoid cells) or breaks through the posterior clinoid process. When this self-decompression occurs, the pressure is temporarily relieved from various portions of the optic chiasm, allowing the sight to return to the retina supplied by those fibers. This accounts for the very peculiar relief from or change in the eye symptoms of the patient. Pituitary headache is probably due to direct pressure upon the capsule of the gland and the intracranial pressure. The patient frequently complains of pain directly in the eyes or eye having perimeter deviation. In two cases, which lasted six months to one and one-half years, respectively, both with unquestionable enlargement of the sella and perimeter signs, with general hormonal signs of pituitarism, there was and had been no headache. In all but one case there were outspoken, general hormonal symptoms and signs—objective changes in the osseous system, localized adiposity (such as the girdle adiposity characteristic particularly of pituitary disorder), polyuria, complete and prolonged amenorrhea and pigmentation, each of which is specifically connected with pituitary disorder. Six subjects had polyuria, and 3 glycosuria. In all cases it was considered a hypophyseal glycosuria on account of its peculiar dissociation from carbohydrate intake and hyperglycemia. In some of these cases the blood sugar was very high, with a normal urine, and in other cases the blood sugar was apparently normal, as in renal diabetes, with variable glycosuria. Classical pituitary adiposity was present in 4 cases, and in 1 case pituitary hibernation occurred.

Of these 13 subjects, with an average duration of  $5\frac{1}{2}$  years, only 3 died. Of the other 10 patients, still living, the duration varied from 1-14 years, and these have been under more or less constant observation. Of these, 2 have been operated upon and a number of others have been advised to have operation, on account of the positive signs of progress of the tumor growth, but have not accepted surgical treatment. A number have been advised against operation on account of the presence of definite symptomatology indicating absence of progression or even regression in size of the neoplasm, as proved by the subsidence of both neighborhood and general intracranial pressure symptoms.

The indications for treatment depend upon the progression of the tumor at the time of observation. If there is evidence of a tumor which has become stationary, as occurs in some of these cases, particularly cyst of the hypophysis, there is no indication for immediate surgical intervention. On the other hand, the treatment for rapidly growing tumor, which shows progressive ocular or sellar signs and evidence of increasing intracranial pressure, should be considered surgical. Possibly one exception to this rule would

be those cases giving an unquestionable specific history with positive physical and laboratory reactions. These subjects might be treated for a limited length of time on specific and x-ray treatment, on the basis of the possibility that the neoplasm is due to gumma of the hypophysis. If this treatment is not effective in the course of 6 or 8 weeks, it would be well to consider surgical intervention. In patients presenting evidence of rapid progression, who do not accept an operation, the only other means of treatment is x-ray and radium. In these cases radium is not very efficient on account of lack of deep penetration. High voltage x-ray treatment, focused upon the hypophysis through the temporal and frontal regions, beneath the hairline, has been effective in the hands of some men, mostly of the foreign schools. With regard to the medical treatment, it has practically no field in these cases, except in a minor secondary rôle in those which have as a result of pituitary tumor a hyposecretion of one or both lobes. Substitution of these preparations to relieve the secondary hormonal signs, such as polyuria, obesity, amenorrhea, hibernation, pituitary headache, etc., may be given. It should always be borne in mind, however, that there is a very slight possibility of activating the pituitary tumor by giving these substances, and for this reason their effect should be observed very carefully, and at any signs or symptoms of hypersecretion this medication should be discontinued.—I. B.

**Surgery of pituitary body.** Frazier (C. H.), Arch. Surg. (Chicago), 1924, 8, 39-61.

Frazier analyzes 18 cases, representing what were regarded as primary intrasellar lesions, for the relief of which a transsphenoidal hypophysectomy was performed. In this series, there were no operative fatalities. Three patients have died in the interim, and in the other cases the results have been satisfactory in 75%. The relative merits of glandular therapy, irradiation and operation are presented. The indications for operation are clearly set forth. Surgical intervention offers an assurance not only of the arrest of visual deterioration, but also of improvement in a considerable proportion of cases. The combination of operation and irradiation will prolong the period of relief or prevent recurrence. The transsphenoidal operation is devoid of serious risk.—J. Am. M. Ass., 82, 822.

**Action of pituitary extract on renal function** (Über die Wirkung der Hypophysenextrakte auf die Nierenfunktion). Fromherz (K.), Arch. f. exper. Path. u. Pharmakol. (Leipz.), 1923, 100, 1-37.

This paper forms an important contribution to our knowledge of the action of pituitary extract on renal secretion. Until now two effects, apparently contradictory, have been described. An injection of the extract made intravenously into the anesthetized animal

causes diuresis. An injection made subcutaneously into the normal animal has an antidiuretic effect in that it delays the excretion of a volume of water taken by mouth; in this connection there is, moreover, the well-known use of the extract to counteract diabetes insipidus. Fromherz now shows that both effects can be obtained either in the normal or in the anesthetized animal. Using dogs from which the urine is collected 2-hourly by catheter, simultaneous subcutaneous injection of pituitary extract and oral administration of water is followed by suppression of urine formation lasting for 6 or 7 hours. If, however, the injection of pituitary extract be intravenous, or, being subcutaneous, precedes the administration of water by 1 hour, there is not only no suppression of urine, but a positive diuresis is observed. Similarly in the anesthetized rabbit a single injection of pituitary extract causes diuresis; if the same dose be slowly infused into the vein diluted in a large volume of the same saline, there is a suppression of the outflow from the ureters so long as the infusion lasts (for example, 1 hour). Fromherz considers that in every case pituitary extract has an antidiuretic effect, sooner or later giving way to a diuretic action. Under some conditions only one of these is observed, while the other escapes notice. He confirms the statement that the concentration of chlorides in the urine is greater while pituitary extract exerts its effect; this effect is primarily renal; changes in the blood (dilution) are secondary.—*Physiol. Abst.*, 9, 23.

**Basal metabolism in the non-hypophyseal adiposo-genital syndrome** (*Le métabolisme basal dans le syndrome adiposo-génital non hypophysaire*). Labbé (M.) Stévenin (H.) & van Bogaert (L.). *Ann. de méd. (Par.)*, 1924, 15, 112-118.

A study of basal metabolism in 10 cases of adiposity combined with genital insufficiency gave 5 well below normal, 2 slightly below and 3 within normal limits.—F. S. H.

**The glucose equivalent of insulin in depancreatized dogs.** Allan (F. N.), *J. Biol. Chem. (Balt.)*, 1924, 59, xxviii.

The glucose equivalent of insulin falls off with increasing dosage of the hormone.—F. S. H.

**Experimental studies in diabetes. Series V. Acidosis. I. The production of diabetic acidosis and coma in dogs.** Allen (F. M.), *J. Metab. Res. (Morristown)*, 1923, 3, 775-795.

The less frequent occurrence of acidosis and coma in dogs with experimental diabetes has been advanced by some workers as an argument against the identity of this form of diabetes and that spontaneously occurring in man. In the present paper Allen presents the protocols of 4 partially depancreatized dogs, all of which developed this complication. Two showed fasting acidosis, whereas



Some factors influencing the response of rabbits to insulin. Blatherwick (N. R.), Long (M. L.), Bell (M.), Maxwell (L. C.) & Hill (E.), J. Biol. Chem. (Balt.), 1924, 59, xxxvi.

Rabbits fed a low carbohydrate base-forming diet are less resistant to insulin than those fed a high carbohydrate acid-forming diet. This is probably not due to glycogen in the tissues. "Education" to insulin convulsions is producible. Data are given which support the hypothesis that the dosage of insulin varies directly with the body weight and not as the square of the weight. Growing rabbits must be gaining steadily in order to give good results with insulin. The animals are used every 7th day. Rabbits which have never received insulin are given sufficient amounts to produce convulsions before they are used for standardization.—F. S. H.

A study of the reaction of normal human subjects to intravenous injections of insulin. Bodansky (A.) & Simpson (S.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, 21, 280.

The blood sugar curve showed a minimum 18 minutes following injection with return to normal at the end of an hour. In overweight subjects the reaction is not so great but recovery is slower. "It is suggested that varying degrees of adiposity as such underlie the differences in the reaction to insulin of animals used in its assay."—J. C. D.

Influence of insulin on the disturbances of the menstrual function in a case of severe diabetes (*Influence de l'insuline sur les troubles de la fonction menstruelle dans un cas de diabète grave*) Carrasco Formiguera (R.), Compt. rend. Soc. de biol. (Par.), 1924, 90, 826-827.

In a patient with amenorrhea and diabetes the menstrual periods were restored after treatment with insulin.—T. C. B.

Blood concentration in insulin hypoglycemia. Drabkin (D. L.), Page (J. H.) & Edwards (D. J.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, 21, 309-311.

Dogs were anesthetized with iso-ethyl-barbituric acid, a drug which does not influence the blood sugar or blood concentration. After large doses of insulin, 20 units per kilo, there was an increased concentration of the blood accompanying the hypoglycemia.  
—J. C. D.

Further purification of insulin and analysis of the product. Doisy (E. A.) & Weber (C. J.), J. Biol. Chem. (Balt.), 1924, 59, xxxiv-xxxv.

Fractionation of crude insulin employing alcohol as the solvent and the phenomenon of isoelectric precipitation have yielded a

product which lies between 0.015 and 0.025mg. per Toronto unit. This purified insulin gives the biuret reaction corresponding to an equivalent weight of peptone. The total nitrogen is 14%. After hydrolysis the ammonia nitrogen is 10% and the amino nitrogen 70% of the total. The tyrosine content is 10% and the cystine 13%. Tryptophane is absent. Values are only approximate. The purified product is rapidly inactivated by trypsin.—F. S. H.

On the preparation and properties of insulin. Somogyi (M.), Doisy (E. A.) & Shaffer (P. A.), J. Biol. Chem. (Balt.), 1924, 59, xxxiii-xxxiv.

The authors use large amounts of strong acid during extraction to insure the solution of insulin and destruction of proteolytic enzymes. The active material is precipitated by ammonium sulfate and later by adjusting the reaction to pH 5. Details will be reported later.—F. S. H.

Action of insulin on thyroidectomized rabbits (*Action de l'insuline sur les lapins éthyroïdés*). Ducheneau (L.), Compt. rend. Soc. de biol. (Par.), 1924, 90, 248-249.

Thyroidectomized rabbits are more sensitive to the hypoglycemic effect of insulin than control healthy animals. The lowering of the glycemia is more marked and the mortality greater.—T. C. B

Improvements in the preparation of insulin. Alkaline extraction of the pancreas. Dudley (H. W.) & Starling (W. W.), Biochem. J. (Lond.), 1924, 18, 147-150.

By a simple modification of the original process of alcoholic extraction of pancreas, namely, by adding sodium bicarbonate to the mixture of minced pancreas and alcohol, the yield of insulin is increased nearly fivefold. An improved technic for the purification of crude insulin by precipitation with picric acid and subsequent conversion of the picrate into soluble hydrochloride is described. At least 90% of the impurities are removed.—F. S. H.

The amount of available insulin in the pancreas of domestic animals. Fenger (F.) & Wilson (R. S.), J. Biol. Chem. (Balt.), 1924, 59, 83-90.

The authors found that the most important factor in insulin production is absolutely fresh glands. It is also advantageous to break up the cell walls as thoroughly as possible in order to release the insulin and render it available for extraction. The mincing should be followed immediately by a brief but efficient grinding process. The disintegrating processes should be continuous up to the moment the macerated tissue is put into the acidulated alcohol and water mixture in order to minimize the action of trypsin.

Freezing does much harm. The amount of insulin in the pancreas of domestic animals varies from 1,500 to 2,200 rabbit units per kilo of fresh gland. The average yield approximates 1,800 units from cattle, hogs and sheep. The methods employed in separating and standardizing insulin are described in detail. Some of the physical and chemical characteristics of purified insulin are pointed out.—F. S. H.

Presence of toxic and insulin-like substances in oranges, grapefruit and lemons. Fisher (N. F.) & McKinley (E. B.), *Proc. Soc. Exper. Biol. & Med. (N. Y.)*, 1924, **21**, 248-249.

The authors have separated a hyperglycemia and a hypoglycemia producing substance from the juice, pulp and rind of the fruits examined. The blood sugar reducing substance resembles insulin rather than glucokinin in its physiological action—J. C. D.

The treatment of diabetic coma with insulin. Foster (N. B.), *Am. J. M. Sc. (Phila.)*, 1923, **166**, 699-709.

A detailed report of 15 cases of diabetic coma. Of these 8 recovered, and of the 8 that recovered 5 were still alive at the time of writing. There seemed to be 3 abnormal conditions which are notable in all cases of diabetic coma: acidosis, desiccation of the tissues, and myocardial weakness. While acidosis is primary and in a sense probably initiates other disorders in the body chemistry, it is also true that death may result from one or both of the secondary factors after the acidosis has been corrected. These other factors demand attention in the treatment of diabetic coma. Acidosis is initiated by failure of the oxidation of glucose. The primary object in treatment is to substitute a carbohydrate metabolism for a dominant and progressively imperfect fat metabolism. Insulin makes it possible to accomplish this end, but only when glucose is available for oxidation when the insulin is given. Therefore, it is logical to use glucose in clysters and in beverages.—J. P. S.

New diets in diabetes. Grote (L. R.), *Zentralbl. f. innere Med. (Leipz.)*, 1924, **45**, 3.

Grote reviews the newer methods of dietetic management for diabetes. Fasting is of use in the beginning of the treatment. Petré's method, using extremely small amounts of proteins (even less than 25 gm.) and very large amounts of fat, gives excellent results. The eventually resulting acidosis is slight and transitory. He believes that the assumption of inevitable ketogenesis from fats is untenable.—*J. Am. M. Ass.*, **82**, 667.

Acetonemia in avitaminosis (Zur Frage der Acetonämie insbesondere bei der Avitaminose). Händel (M.), *Biochem. Ztschr. (Berl.)*, 1924, **144**, 258-264.

Only traces of acetone are to be found in blood of normal persons or animals. The greatest acetonemia was found in dogs 5 or more days after extirpation of the pancreas and in dogs which had been fasted for many days, during which daily injections of phlorizin had been made. A lower degree of acetonemia was found in animals which were simply fasted or treated with the drug. The increase in the acetone bodies in the blood comes largely from beta-oxybutyric acid.—F. S. H.

The respiratory quotients of normal rabbits after the administration of insulin. Hawley (E. E.) & Murlin (J. R.), *J. Biol. Chem.* (Balt.), 1924, 59, xxxii-xxxiii.

The respiratory quotient is raised when the blood sugar is lowered by insulin. The object of the experiments was to see whether a purer insulin would produce higher quotients without a depression of the total metabolism, and whether a definite impurity which raises blood sugar (glucagon) would depress the respiratory quotient. The evidence obtained supports the suppositions.—F. S. H.

Old and new treatment of diabetes from a statistical point of view. Heiberg (K. A.), *J. Metab. Res.* (Morristown), 1923, 3, 677-678.

The author briefly compares the results of diabetic treatment of diabetes by the old (Allen and Sherrill) method and the new low protein and high fat diet of Petré. He concludes from the statistics of these various observers that the unmodified method of Allen is superior to that of Petré.—I. M.

Studies of the effect of exercise in diabetes. I. Change in acid-base equilibrium and their relation to the accumulation of lactic acid and acetone. Himwich (H. E.), Loebel (R. O.) & Barr (P.), *J. Biol. Chem.* (Balt.), 1924, 59, 265-293.

These observations were made on man. In the diabetics which were studied there was no evidence that during exercise the body is unable to produce lactic acid or to dispose of it after it is formed. There is no indication that the chemical mechanism of muscular contraction need be anything else than the breakdown of carbohydrate to lactic acid which is utilized in muscular work in normal man. The experiments demonstrate that in the moderately severe diabetic subject short periods of exercise lead to the formation of lactic acid in large amounts and do not cause accumulation of acetone bodies in the circulating blood. From the theoretic point of view the experiments are considered as inconclusive. All the patients were capable of utilizing some carbohydrate. It is considered as quite possible that the subjects studied retained enough of the normal functions of carbohydrate utilization to perform the muscular contractions which were required of them by the usual mechanism and for that reason exhibited the normal accumulation of

lactic acid. A different mechanism might be conceivably employed in completely diabetic patients. In the human subject with complete diabetes exercise sufficient to cause accumulations of lactic acid in the blood is not feasible. Experiments upon lactic acid and acetone production during exercise of completely diabetic animals are in progress. Only hints concerning the effect of exercise upon the well-being of diabetic patients can be obtained from the observations. The two kinds of exercise used were such as might be used by any ambulant diabetic during the course of his daily life routine. No attempt was made to carry the exertion to the point of fatigue. Both types of exercise (short run and longer vigorous walk) seem to produce marked acid production and reduction of alkaline reserve. No alarming depletion of the latter obtained. However, none of the patients had particularly low values at the beginning. The observations do not exclude the possibility of serious damage.—F. S. H.

**Studies on carbohydrate metabolism. II. On the preparation of an anti-diabetic hormone from yeast. Part 1.** Hutchinson (H. B.), Smith (W.) & Winter (L. B.), *Biochem. J. (Lond.)*, 1923, **17**, 683-692.

It is shown that a substance may be extracted from yeast which has an effect similar to that of insulin on the blood sugar of normal animals. When convulsions occur as the result of the injection of this substance, the animals may be restored to normal by injections of glucose. Samples of yeast from different sources yield varying amounts of glucokynin. By allowing the yeast to ferment under different conditions, it is found that only in the case of an originally active yeast is the glucokynin formation increased under certain cultural conditions.—F. S. H.

**Studies on carbohydrate metabolism. III. On the formation of an anti-diabetic hormone by the action of a bacillus (Preliminary communication).** Hutchinson (H. B.), Smith (W.) & Winter (L. B.), *Biochem. J. (Lond.)*, 1923, **17**, 764-767.

A portion of yeast was placed on nutrient agar and a pure culture of a bacillus obtained. Previous tests had shown that an extract of the yeast would cause a slight fall in blood sugar. The bacillus was then cultured and was found to be of the coli form. During the growth of this an insulin-like substance is formed. Injection of the extract into rabbits causes hypoglycemic convulsions which are relieved by glucose.—F. S. H.

**Differential diagnosis of diabetes.** John (H. J.), *Am. J. M. Sc. (Phila.)*, 1923, **166**, 275-280.

In the diagnosis of diabetes the patient's ability to utilize carbohydrates should be determined. This cannot be determined from an examination of the urine alone. The establishment of the glu-

coarse tolerance curve is the only method by which the ability of the individual to utilize carbohydrates can be determined with certainty.

—J. P. S.

A report of sixty-four cases of diabetes mellitus treated with insulin. Jonas (L.), *Am. J. M. Sc. (Phila.)*, 1923, 166, 687-699.

These cases were divided into three groups: (1) mild cases with no diacetic acid in the urine on admission; (2) cases with reduced  $\text{CO}_2$  content of the plasma and with diacetic acid in the urine but with normal plasma pH; and (3) cases with a lowered plasma pH in addition. There were 47 subjects in the first group, 6 in the second and 11 in the third. For treatment these cases were divided into mild and severe, the latter including the second and third groups mentioned above. Five of the 17 patients were in coma when admitted; 6 suffered from acute infections of various kinds. The insulin dosage in the mild cases varied from 5 to 30 units a day; in the severe cases, from 30 to 45 units per day. Of the 5 patients that entered in coma, 2 died within an hour after admission; the other 3 recovered after treatment with insulin. The efficacy of insulin in the control of diabetes during acute infections was striking in all 6 cases; of these, 4 subjects had diabetic gangrene, 1 had carbuncles and 1 lobar pneumonia. The patients treated with insulin showed a drop in blood sugar concentration during the day and a rise at night. The minimum value occurred in the afternoon or early evening and coincided with the time at which hypoglycemic symptoms, characterized by weakness, sweating and headaches, were noted. The amount of insulin sufficient to balance the carbohydrate of a meal might to advantage be given after the meal rather than before it. One of the effects of insulin, particularly in the undernourished, has been gain in weight. This gain is not immediate, however, even on liberal diets.—J. P. S.

The effect of insulin upon the reducing substance in the cerebrospinal fluid of normal rabbits. Kasahara (M.) & Uetani (E.), *J. Biol. Chem. (Balt.)*, 1924, 59, 433-436.

There is a decrease in the concentration of the reducing substance in the cerebrospinal fluid after subcutaneous administration of insulin. There is some parallelism of the concentration of the reducing substance both in the fluid and blood.—F. S. H.

The effect of insulin upon the complement derived from insulinized guinea pigs for the Wassermann reaction. Kretschmer (O. S.), *J. Lab. & Clin. M. (St. Louis)*, 1924, 9, 442-443.

It is shown that the pooled serum of guinea pigs made hypoglycemic by treatment with insulin shows no appreciable change in its complementary titer in comparison with pigs not so treated, and retains this property for fully 30 days.—I. B.

The use of fat in diabetes mellitus and the carbohydrate-fat ratio. Ladd (W. S.) & Palmer (W. W.), *Am. J. M. Sc. (Phila.)*, 1923, 106, 157-169.

The carbohydrate-fat ratio at which the ketone bodies fail to be completely oxidized is apparently fixed, and is the same for both normal and diabetic persons. For practical purposes, the carbohydrate-fat ratio of 1 : 4, calculated from the formula

$$\frac{F}{G} = \frac{\text{Fat in grams}}{0.58 \text{ gm. P.} + \text{gm. CH}}$$

(in which F indicates fat; G, available carbohydrate; P, protein; and CH, carbohydrate) is the most serviceable in the construction of diets where it is desired to obtain a maximum caloric intake with a minimum in the form of carbohydrate. Relatively large amounts of fat may be used in diabetic diets without injury to the patient. *There are, however, the following qualifications:* (a) *The urine can be freed from sugar and acetone bodies more quickly by under-nutrition to the point of starvation than by any diet where exogenous fat is substituted for the amount of body-fat assumed to be burned;* (b) *there is need, as yet, to follow carefully any severe case of diabetes where the ratio is not well within the limits of 1:4;* (c) *in the presence of infection or an already severe ketonuria, high-fat diets are not advised.*—J. P. S.

Action of insulin in Graves' disease (*Action de l'insuline sur le syndrome basedowien*). Lépine (J.) & Parturier (G.), *Compt. rend. Soc. de biol. (Par.)*, 1924, 90, 269.

All the symptoms of exophthalmic goiter were improved in a man of 48 by injection of insulin for 10 days.—T. C. B.

The influence of insulin on the respiratory exchange and the temperature of the rabbit (*Influence de l'insuline sur les échanges respiratoires et la température du lapin*). Matton (M.), *Compt. rend. Soc. de biol. (Par.)*, 1924, 90, 361-364.

Injection of insulin in rabbits does not alter the CO<sub>2</sub> during the first half hour, after which there is a progressive diminution of CO<sub>2</sub> and of the temperature. At the onset of convulsions there is a temporary augmentation.—T. C. B.

Insulin from fish. McCormick (N. A.) & Noble (E. C.), *J. Biol. Chem. (Balt.)*, 1924, 59, xxix.

Large islets of insulin-containing tissue occur in the cod and halibut close to the gall-bladder. The insulin obtained from these sources can be used clinically with safety. In several of the species examined it was found that extracts of liver prepared as described contained hyperglycemic producing principles.—F. S. H.

Some favorable effects from the alimentary administration of insulin. Murlin (J. R.), Sutter (C. C.), Allen (R. S.) & Piper (H. A.), *Proc. Soc. Exper. Biol. & Med. (N. Y.)*, 1924, **21**, 338-340.

This report gives a table showing the results of duodenal administration of insulin in 2 cases and administration in enteric coated capsules in 2 others. The results are encouraging in both instances.—J. C. D.

Does insulin increase tolerance? Newburgh (L. H.), *Boston M. & S. J.*, 1924, **190**, 352-355.

The author fails to find evidence that insulin increases the sugar tolerance. He supports his conclusions with several case reports.—J. C. D.

Influence of insulin on heat loss in the rabbit (*Influence de l'insuline sur la déperdition calorique chez le lapin*). Noyons (A. K.), Bouckaert (J.) & Sierens (A.), *Compt. rend. Soc. de biol. (Par.)*, 1924, **90**, 365-368.

The first symptom to appear after subcutaneous injection of insulin is a lowering of temperature—even before the depression which precedes the onset of the hypoglycemic crisis. The caloric loss remains that of an animal in repose during the first few hours after the injection. At the end of this period convulsions develop. The curve of heat loss and body temperature descend together and the animal dies in a state of hypothermia. The injection of glucose counteracts these conditions.—T. C. B.

The effect of insulin on the oxygen saturation of hemoglobin. Olmsted (J. M. D.) & Taylor (A. C.), *J. Biol. Chem. (Balt.)*, 1924, **59**, xxx.

A reduction of hemoglobin saturation in the blood is evidently associated with the convulsions caused by insulin hypoglycemia.

—F. S. H.

The value of weight curves in determining the severity of diabetes. Olmsted (W. H.), *Med. Clin. N. Am. (Phila.)*, 1924, **7**, 1631-1644.

Emphasis is laid on the importance of taking a careful history of every diabetic patient, a valuable procedure in determining the probable severity of the case. In diabetics under 35 the disease is usually severe, with rapid reduction in weight. If, however, the young diabetic is of weight normal or above, it is safe to assume that the disease is of mild degree, or that true diabetes does not exist. This is especially true if there has been glycosuria without loss of weight for a period of three or more years. In diabetics past the age of 40 the disease is usually mild, and 75% are overweight. The weight actually lost below the patient's normal standard is the really significant factor to be taken into account.—I. B.



On the normal urine sugar curve in normal individuals, borderline diabetics and severe diabetics under insulin treatment. Page (I. H.), J. Lab. & Clin. M. (St. Louis), 1923, 8, 631-651.

Observations on the hourly urine sugar curve were made on normal subjects, borderline diabetics, severe diabetics under insulin treatment, renal diabetics, subjects with borderline glycosuria under insulin treatment and with hyperthyroidism. The author discusses the use of insulin in borderline glycosuria and describes a standard technic for the determination of the hourly sugar curve. He believes that an examination of the hourly sugar curve will disclose cases of mildly pathological sugar metabolism that would ordinarily be overlooked. This method, on the one hand, detects abnormally high sugar wastage, and, on the other, warns of dangerously low sugar secretion, hence offers an almost ideal method for the control of cases of diabetes under insulin treatment.—I. B.

Action of pancreatic extracts on diabetic animals (*Recherches expérimentales sur l'action des extraits pancréatiques dans les phénomènes du diabète chez les animaux*). Paulesco, Bull. et mém. Soc. med. d. hôp. de Par., 1924, 48, 329-333.

Paulesco claims that successful preparation of effective extract of pancreas was made before the work of Macleod and his collaborators. He refers to his article in Arch. internat. de physiol. for August, 1921. The author was granted patent No. 6254 from the Minister of Industry and Commerce of Roumania for "La Pancréine et le procédé de sa fabrication."—F. S. H.

On the purification of insulin. Piper (H. A.), Allen (R. S.) & Murlin (J. R.), J. Biol. Chem. (Balt.), 1924, 59, xxxii.

The yield of crude insulin is enormously increased by re-extraction of the precipitates. In spite of all precautions much of the compound is lost in the process of purification.—F. S. H.

The incidence of diabetes mellitus in diseases of the gall bladder and its passages (biometrical study). Rabinowitch (I. M.), Canad. M. Ass. J. (Toronto), 1924, 14, 296-297.

Analysis of 46,000 hospital cases showed that nine times as many patients with diseases of the gall bladder and its passages (including cholecystitis and cholelithiasis) had diabetes as would be expected if the influencing factors were completely independent.

—A. T. C.

Ketosis and the respiratory exchange in diabetes. Richardson (H. B.) & Ladd (W. S.), J. Biol. Chem. (Balt.), 1924, 58, 931-968.

The results of these intensive experiments on human subjects indicate that the fatty acid-glucose ratio, calculated from the data

observed with the respiration calorimeter, was parallel with the excretion of the acetone bodies. The threshold of ketosis was found near a ratio of 1.5 to 1.0. This ratio corresponds theoretically to the presence, during oxidation, of 1 molecule of keto-acid for every molecule of glucose. This parallelism is evidence that the respiratory quotient in diabetes is a true measure of oxidation. Diabetic patients were often able to take without undergoing ketosis diets containing a larger proportion of ketogenic substances than is called for by the ratio. This was because the proportions of foodstuffs oxidized were not the same as those ingested. The fall of ketosis observed in diabetic patients as a result of fasting is accounted for by the simultaneous drop in the fatty acid-glucose ratio calculated from the calorimeter data. It was due primarily to a decrease in the total metabolism with a consequent diminution in the metabolism of fats and protein. At the time of fasting there was little or no increase in the total quantity of glucose oxidized when this was computed as being derived from protein and the glycerol of the fat as well as from the carbohydrate undergoing metabolism during the period. Fasting reduces the blood sugar chiefly by depleting the endogenous source of glucose. There is often an increase in the oxidation of glucose during the subsequent period of restricted diet, but this is not necessarily due to the fast.—F. S. H.

The influence of insulin on phlorhizin diabetes. Ringer (M.), *J. Biol. Chem. (Balt.)*, 1923, 58, 483-501.

Phlorhizinized dogs were treated with insulin. An extensive study of the sugar excretion, the D:N ratio and the basal metabolism was made. From the results it is concluded that insulin injected into completely phlorhizinized dogs results in an oxidation of glucose. A maximum oxidation of 0.95 gm. of glucose per unit of insulin was obtained. Evidence is adduced to show that glucose was also stored as glycogen. Insulin reduced the protein metabolism from its high diabetic level. It caused the disappearance of ketone bodies and reduced the heat production by 2 calories per hour. The bearing of these data on the mechanism of phlorhizin diabetes is discussed. The argument is brought forth that the striking effect of insulin in correcting diabetes of a phlorhizinized dog indicates that phlorhizin transitorily injures the pancreas by preventing the production of the antidiabetic hormone. The use of phlorhizinized dogs in the assay of insulin is proposed.—F. S. H.

The treatment of diabetes with insulin. A report of the methods followed and the results obtained in the first one hundred cases. Sansum (W. D.), Blatherwick (N. R.), Smith (F. H.), Long (M. L.), Maxwell (L. C.), Hill (E.), McCarty (R.), & Cryst (J. H.), *J. Metab. Res. (Morristown)*, 1923, 3, 641-676.

Part of the insulin used was obtained from the Eli Lilly Co.,

but about five-sixths of the quantity used was made by the authors themselves according to the method of Collip. The objects of treatment constantly before them were: (1) that the patient should be kept continuously "sugar free," and that the blood sugar should be normal; (2) that the patient should be kept continuously free from acidosis; and (3) that the patient should be nourished as evidenced by a satisfactory weight. When diet alone was inadequate for the accomplishment of these aims insulin was used also. Four conditions should be fulfilled, according to the authors, in the treatment of diabetes with insulin: (1) the sugar utilizing power of the insulin in grams per cubic centimeter should be known; (2) the patient's natural tolerance should be determined in grams of sugar formers; (3) the exact diet should be known; and (4) the dosage of insulin may then be adjusted to make up the difference between the sugar formers of the proposed diet and those of the patient's natural tolerance. The symptoms and treatment of insulin over-dosage, the necessity for education of the patient and a detailed outline of diets used are discussed. The results of insulin treatment obtained are confirmatory of the results of others working in this field. Patients with insulin plus diet therapy developed an increase in tolerance more quickly than those on diet alone.—I. M.

Some chemical reactions of the substance containing insulin. Shonle (H. A.) & Waldo (J. H.), *J. Biol. Chem. (Balt.)*, 1924, 58, 731-736.

From the discursive data given in this paper it is concluded that the pancreatic substance containing insulin appears to be a complex mixture of proteoses, which give typical protein reactions and from which it has as yet been impossible to isolate a simple substance or to detect a chemical reaction that is characteristic of the physiologically active constituent.—F. S. H.

The duration and magnitude of the hypoglycemia after insulin. Severinghaus (E. L.), Kirk (Elizabeth) & Heath (H. J.), *Am. J. M. Sc. (Phila.)*, 1923, 166, 677-686.

Eight students who had not had breakfast on the morning of the tests were divided into three groups and given 4, 8 and 10 units of insulin, respectively. Blood sugar was estimated by the method of Folin and Wu. Another group of students who had not had breakfast on the morning of the experiment was given 100 grams of glucose dissolved in 200 cc. of water to which had been added the juice of one lemon. Their sugar tolerance was investigated, the sugar content of the urine being determined by the method of Folin and Berglund. Two or three days later the same students were submitted to the same test except that immediately after the sugar solution had been swallowed, each was given an injection of insulin varying from 8 to 16 units. From their experiments the authors

conclude that in normal human subjects the extent and the duration of the hypoglycemia after the injection of insulin are so variable that the result cannot be predicted from the dose per kilo of body weight. The extent of the hypoglycemia and the duration of the low level are roughly parallel to the dose of insulin. The depression of the sugar tolerance curves by insulin is not uniform in type or extent. With increasing dosage of insulin both the extent and the duration of the hypoglycemia are increased. The blood sugar concentration at which symptoms of overdosage of insulin appear varies in different individuals in the region of from 40 mg. to 65 mg. per 100 cc. of blood. The concentration of sugar in the urines of normal subjects does not follow the blood sugar level with or without insulin. It is related more closely to the urine volume. The treatment of diabetics with small doses of insulin at intervals of not less than 6 hours is preferred to the use of larger doses at very long intervals, or of smaller doses at too short intervals. Intranasal application of insulin is without effect.—J. P. S.

Some attempts to administer insulin per rectum (*Quelques essais d'administration de l'insuline par le rectum*). Stenström (T.), *Compt. rend. Soc. de biol. (Par.)*, 1924, 90, 518-520.

In mice ten times the lethal dose of insulin, given by rectum, is without effect, due to the destructive action of the ferments of the intestinal contents on insulin.—T. C. B.

On the blood phosphates after insulin convulsions. Winter (L. B.) & Smith (W.), *J. Physiol. (Lond.)*, 1924, 58, 327-333.

Rabbits have been successfully treated in insulin convulsions by adrenalin, pituitary extract and glucose. After adrenalin the inorganic phosphate usually regains the normal level quickly and falls again. With pituitrin the effect is variable. After glucose the normal volume is not regained for some time.—T. C. B.

The action of ammonium hydroxide and other alkaline compounds upon insulin. Witzemann (E. J.) & Livshis (L.), *J. Biol. Chem. (Balt.)*, 1923, 58, 463-474.

The results described in this paper show that insulin is more or less completely inactivated at room temperature by 0.5 or 0.7 N ammonium hydroxide in the course of some days, and that its original activity is usually quickly restored on acidification with hydrochloric acid. It was also found that sodium and potassium hydroxides even at 0.1 N concentration irreversibly inactivate insulin at room temperature. Sodium carbonate and bicarbonate and disodium phosphate had almost no effect. Some exploratory experiments on the effects of mixed alkalis indicated that the above reactions are also subject to secondary accelerative and retarding effects, depend-

ing upon the mixture used. They suggest a tautomeric rearrangement.—F. S. H.

Some milder forms of diabetes with special reference to mild diabetes in elderly persons with arteriosclerosis. Woodyatt (R. L.), South. M. J. (Birmingham), 1924, 17, 145-153.

The author calls attention to a type of case in which the patient shows some sugar in the urine over a long period, but no thirst and no loss of weight. He is able to burn most of the sugar taken in, even though that amount be large, but is not able to burn it all even when the intake is reduced to a very low point. Insulin has little influence in such cases. Care should be taken not to cripple such patients by reducing the diet when the sugar leakage is not a dangerous symptom. Dietary methods for testing this with case histories and charts are included in the article.—J. C. D.

Parathyroids in anthropoid apes (*Epithelkörperchenbefunde bei Menschenaffen*). Arndt (H. J.), *Ztschr. f. Anat. u. Entwicklungsgesch.* (Berl.), 1923, 68, 514-522.

Gross and microscopical description of the parathyroids in chimpanzees. Some literature is cited.—A. T. R.

Experiments with an active extract of parathyroid. Ellingson (E. O.), Bell (A. W.) & Hanson (A. M.), *Proc. Soc. Exper. Biol. & Med.* (N. Y.), 1924, 21, 274-275.

By boiling finely divided ox parathyroids with dilute HCl the authors obtained an extract which they think contains the active principle of the parathyroid. After its administration dogs showing convulsions recovered and it has been beneficial in gastric, duodenal, and varicose ulcers and several other types of chronic inflammation. Its effects resemble those following a relative increase of the ionic calcium in the blood. The active principle itself has not been isolated.—J. C. D.

Are guanidines present in the urines of parathyroidectomized dogs? Greenwald (I.), *J. Biol. Chem.* (Balt.), 1924, 59, 329-337.

By using a carefully controlled and new method of chemical analysis Greenwald was unable to demonstrate the presence of more than 0.5% of guanidine nitrogen (in terms of total nitrogen) in the urine of parathyroidectomized dogs. From the fact that a high percentage of recovery of added guanidine to the urine was attainable by the new method and other arguments given in the body of the paper, it is evident that but little justification is to be had for considering that parathyroid tetany is due to guanidine intoxication until further evidence is available. No theory of the causation of tetany can be considered adequate if it fails to take into account

the changes in calcium and phosphorus in the blood and urine as being intimately connected with the sequence of symptoms observed.

—F. S. H.

Treatment of chronic postoperative tetany by intravenous injections of calcium chloride and injections of parathyroid extract in large doses (*Le traitement de la tétanie chronique post-opératoire par les injections intraveineuses de chlorure de calcium et les injections d'extrait parathyroïdien à hautes doses*). Sainton (P.), Bull. et mém. Soc. méd. d. hôp. de Par., 1923, 47, 1576-1578.

The case is reported of a woman of 35 with a large goiter. This was removed and 3 days later tetany set in, appearing at 8-day intervals. Although the attack could be alleviated by ingestion of calcium chloride, the situation continued for four years with increasing involvements. Intravenous injection of 1 gram of the calcium compound in 3 cc. was then attempted with brilliant success, insofar as aborting impending attacks. The solution was diluted from 3 to 10 cc., however. Later on specially prepared extracts of the parathyroid glands were administered intravenously, beginning with a dose equivalent to 0.05 gram and gradually raising it to 0.15 gram. The attacks disappeared completely following this intensive medication.→F. S. H.

Studies on the physiology of the parathyroids. Salvesen (H. A.), Acta med. Scand. (Stockholm), 1923, Suppl. 6, 5-159.

Salvesen carried out an elaborate metabolic study on 7 dogs with partial and 10 with complete parathyroidectomy. He concluded that the drop in blood calcium caused by parathyroidectomy is not due to anesthetics or acidosis. Parathyroidectomy causes no hypoglycemia. The observation that the alkali reserve decreases and the acid excretion increases indicates that there exists no alkalosis after parathyroidectomy. The characteristic feature in the chemistry of parathyroid insufficiency is the drop in blood calcium. The beneficial action of calcium injections on the symptoms of tetanic dogs is so short because the calcium disappears rapidly from the blood. Completely parathyroidectomized dogs can be preserved by calcium treatment and pass into a state of latent tetany. Latent tetany is characterized by a low blood calcium. It is the withdrawal of milk which is responsible for the dietary production of tetany in latent tetanic dogs. Milk prevents tetany by its calcium content. The cause of the lowered glucose tolerance in parathyroidectomized dogs is the decrease in blood calcium. There is a relation between sugar metabolism and the calcium-phosphorus metabolism. Guanidin acts as a convulsive poison without altering the calcium or phosphates of the blood. All the symptoms of parathyroid insufficiency are due to calcium deficiency, which is indicated by the drop in serum calcium. Calcium deficiency causes dysfunction of probably all organs. The

calcium deficiency is due to increased excretion of calcium through the intestines. The cause of this "lowered threshold" is not known. It is not caused by guanidin poisoning. The parathyroids control the calcium level of the blood and by doing so they influence the function not only of the muscle and nerve tissue, but probably of all organs and all cells. How this control is exerted is not known. Life is under certain conditions (calcium administration) possible without the parathyroids. Infantile tetany is probably due to an existing parathyroid insufficiency. Epilepsy, eclampsia and paralysis agitans are not due to parathyroid insufficiency. A good working bibliography and review of the literature are included.—R. G. H.

The relation between calcium and protein of serum in tetany due to parathyroidectomy. Salvesen (H. A.) & Linder (G. C.), *J. Biol. Chem. (Balt.)*, 1923, 58, 635-639.

It was found that the plasma protein content of the blood is not affected by parathyroid removal and the consequent tetany in dogs. The calcium content dropped. This is taken as an indication that the calcium decrease in tetany is not due to a primary decrease in the protein bound calcium, but is caused by a decrease in the diffusible fraction.—F. S. H.

A contribution to the study of the pineal body. Izawa (Y.), *Am. J. M. Sc. (Phila.)*, 1923, 166, 184-196.

A report of a study of 4 pinealectomized chickens (3 males and 1 female). Izawa concludes that pinealectomized young cocks grow more rapidly than the controls, begin to crow prematurely, and show an earlier development of comb and testes. Pinealectomized young hens likewise reveal a premature development of ovary and Fallopian tube. In pinealectomized chickens the endocrine organs, except for the sex glands, show nothing abnormal, or only slight differences, as compared with those of the controls. It appears, therefore, that the pineal body's chief function is to repress the premature development of the sex organs in the female as well as in the male. The details of the results upon which the above conclusions are drawn are tabulated, and from this table the following facts may be cited: one pinealectomized cock 210 days old, weighed 1820 grams, its testes weighed 14.3 grams, and the relative weight of testes in grams to a kilogram of body weight was 7.85; the control of the same age weighed 1200 grams, its testes weighed 1.49 grams, and the relative weight of testes in grams to a kilogram of body weight was 1.24. The corresponding weights in a second pinealectomized cock 251 days old were 1950 grams, 18 grams, and 9.7, respectively; while the control of the same age showed corresponding weights: 1600 grams, 7.0 grams, and 4.3, respectively. The body weight of the pinealectomized hen was about 40% greater and

that of the ovaries slightly more than 100% greater than the corresponding weights in the control hen of the same age.—J. P. S.

Pineal gland secretion in man and some animals (*Contributo allo studio della glandola pineale nell'uomo e in alcuni animali*). Clemente (G.), *Endocrin. e patol. costituz.* (Roma), 1923, 1, 44-47; abstr., *Ber. ü. d. ges. Physiol.* (Berl.), 1924, 23, 447.

In chronic diseases, especially those which influence circulation, the pineal gland undergoes regressive variations which accompany similar changes in the hypophysis. In animals (rabbits, porpoises) in which the pineal had been removed pregnancy nevertheless occurred. Young animals in which the thyroid gland had been removed showed premature development of the secondary sexual characteristics and of the testes.—M. D. G.

Further observations upon the shadows of the thymus and the heart. De Buys (L. R.) & Samuels (E. C.), *South. M. J.* (Birmingham), 1924, 17, 260-264.

The observations were carried out in the first year of life. The points of endocrine interest are that the thymus and heart shadows are independent in size and position and that the thymus shadows may undergo changes in size without any visible symptoms in the patient.—J. C. D.

The respiratory exchange of rats without spleens (*Beiträge zur Physiologie der Drüsen*. 60. L. Asher. Erneute Untersuchung über den respiratorischer Grundumsatz normaler und milzloser Ratten). Takahashi (Y.), *Biochem. Ztschr.* (Berl.), 1924, 145, 130-153.

These studies indicate that splenectomy lowers the respiratory exchange. The presence or absence of iron in the food has no perceptible effect. The nitrogen excretion of the rats was increased by splenectomy in the majority of cases. Splenectomized rats respond more strongly to thyroid feeding than normal animals.—F. S. H.

The effects of extirpation of the thymus (*Sugli effetti della timectomia*). Pighini (G.), *Biochem. e terap. sper.* (Modena), 1922, 9, 207-219.

Before puberty the thymus is indispensable to the nuclein lipid and calcium metabolism. This is demonstrated by surgical extirpation, vagotomy, x-rays or radium, adrenalin intoxication, or a diet deprived of vitamin B.—P. M. N.

An epidemic of acute goiter in a children's home. Adams (E. W.) & Crossley (H. N.), *Lancet* (Lond.), 1923, ii, 500.

A description is given of a small outbreak of acute goiter occurring in one cottage out of a colony of 9 constituting a Children's



Cottage Home. The homes were situated near the village of Wardle. The authors state that the chronic form of goiter seems to be rife among the children of all the cottages, but the acute epidemic was limited to one. There were 8 occupants, boys between the ages of 4 and 10 years, and all were affected. The adult staff escaped. There was no complete record of the previous thyroid state, but one of them was known to have a somewhat enlarged thyroid. On January 10 the boy who had previously had a slight swelling of the thyroid developed a very marked enlargement. On the 12th a similar enlargement was noticed in 2 other boys, and on the 13th the remaining 5 were affected. The right lobe was invariably more affected than the left, and there were no glandular enlargements. The swelling was soft, elastic, painless and non-inflammatory, and in some there were carotid thrills and enlarged venules. The temperature was normal and remained so, and the general health was unimpaired. The bacteriological reports on the throats were negative as regards diphtheria, but gave the predominating organisms as streptococci. After a period varying from 5 to 7 days the thyroids began to subside. The subsidence continued for about a fortnight and then passed into a stationary period. By February 1, one of the cases had returned to normal. On March 6, 3 of the thyroids would not have attracted attention, while in 4 of the others it was only slight. In only one did the enlargement remain considerable. On May 22, 5 of the thyroids were normal, 2 were very slight, and in 1—the boy in whom the condition had started—there was still an appreciable enlargement. No definite etiological factor could be determined at the cottage. The only infection had been a slight epidemic of measles which had cleared up a month before. Goiter is endemic in the district and is not uncommon among the children. In the cottage population of 83 children there were 33 cases of chronic thyroid enlargement as compared with 30 cases among the 249 school children in the neighborhood, thus showing that there was a greater tendency for the chronic variety in these cottages. No differences were determined between the conditions of life in this cottage and those of the other cottages.—*Med. Sc.*, 10, 57.

**Modifications of lipid content of the liver after thyroidectomy** (*Sulle modificazioni del contenuto in liquidi del fegato dopo la tiroidectomia*). Artom (C.), *Arch. di sc. biol.* (Napoli), 1923, 5, 22-43.

It is concluded from a study of their experiments that thyroid deficiency causes modifications of fatty acids and fat metabolism.

—P. M. N.

**Effect of polar ligations upon the remaining lobe of thyroid gland after removal of one lobe.** Barber (W. H.), *Proc. Soc. Exper. Biol. & Med.* (N. Y.), 1924, 21, 239-240.

This is based on a study of 32 dogs. Very few of the glands

involved remained normal after the operation. Degenerative changes were found likewise in two-thirds of the parathyroids seen.

—J. C. D.

**Exophthalmic goiter.** Barker (L. F.), *Internat. Clin. (Phila.)*, 1924, 1, s. 34, 1-16.

This is a clinical lecture on exophthalmic goiter detailing the history and treatment of an exemplifying case. The diagnosis of the disease is easily made in the presence of more than two cardinal symptoms. Toxic adenoma may resemble Graves' syndrome; in the former condition the shelling out of the adenoma by the surgeon results in clear-cut recovery, while treatment of exophthalmic goiter is not quite so precise. Treatment frequently results in subsidence of symptoms, but recurrence is common, and though many are restored to ordinary health and to economic productivity, all require most careful medical supervision throughout life. Exophthalmic goiter is a pluriglandular endocrinopathy, with involvement also of the vegetative nervous system and often of the higher cerebral centers. Barker believes that these individuals possess a basic predisposition to the disease, superimposed upon which psychic trauma, focal infection and other known and unknown factors may serve as exciting causes, bringing to the surface the entire symptom-complex. Surgical treatment, though associated with a much lowered operative mortality rate than heretofore, still carries with it the danger of such post-operative events as acute hypothyroidism, accidents of anesthesia, etc. In medical as well as in surgical treatment, physical and mental rest are of primary importance and should be instituted early. Diet, hydrotherapy, drugs, psychotherapy, and roentgenotherapy play their parts. The fattening of the subject under treatment seems desirable.—I. B.

**Auricular fibrillation in goiter.** Baumgartner (E. A.), Webb (C. W.) & Schoonmaker (H.), *Arch. Int. Med. (Chicago)*, 1924, 33, 500-512.

The authors report 3 cases and review the literature. In summary they say: "Germain Sée, in 1878, described irregular, rapid pulse and heart in cases of goiter in which there was probably fibrillation. Twenty cases, besides a series of 18 by Hamilton and figures from other clinics, have been reviewed. Fibrillation may occur in hyperthyroidism, in both adenoma and exophthalmic cases, and may be paroxysmal or permanent for months or years. These patients should be given digitalis as other patients with fibrillation are given it, and operation should be performed even if there is fibrillation. We believe, as was stated in Schoonmaker and Webb's report, that the 'gravity of the heart condition relative to thyroidec-tomy has been repeatedly overestimated, resulting in delay in operation and in a borderline dangerous myocardial insufficiency.' "

—R. G. H.

The roentgen rays in thyroid therapy. Bierman (M. I.), Minnesota Med. (St. Paul), 1923, 6, 322.

The effects of radiation upon thyroid tumors as well as upon other neoplastic tissue formations are primarily direct, acting on the cells themselves. The rays affect the protoplasm as well as the nucleus of the cell, but the interference with the nucleus is usually of much greater significance for the function of the cell than the localized changes in the cytoplasm, as any marked interference with the nucleus results in the death of the cell. The changes produced in the cells are attended by no risk whatever to the patient provided that the ordinary precautions peculiar to x-ray treatment are observed. It is true that the surgical removal of the thyroid will produce results much more rapidly than roentgen ray treatment; but the uncertainty of improvement, the dangers of operation, and the advisability of first using less extreme measures of treatment will militate against operative interference in favor of radiation. Radiation is the treatment of choice in all types of toxic goiter. The author uses an 8 or 9-inch spark gap; 3 to 6 mm. aluminum filter; cross-fire method; repeated at intervals of 2 to 3 weeks. It is not advisable to produce even a mild erythema and it is important to maintain a check on the effects of radiation by observations of the metabolic rate. When this decreases rapidly to 25 or 30% below normal it is well to discontinue treatment. The changes produced by x-ray continue to exert their influence for as long as two to three months after the last treatment and if treatment were continued until the metabolic rate reached normal the final result would be a negative rate or hypothyroidism. The treatment of thyroids by roentgen ray is necessarily a long drawn out procedure extending over many months and at times even requiring two or three years for a complete cure, and the treatment is rather of benefit only in selected cases which show undoubted metabolic hyperactivity. The adenomatous and exophthalmic types are especially favorable. Other forms such as simple goiter, colloid goiter, the cystic goiter, and the goiter of adolescence are not proper subjects for roentgen ray treatment.—Radiology, 1, 127.

Disturbances in Metabolism. I. Variations in protein metabolism as indicated by sulfur excretion. Goiter. Craig (J. Mc.) & Harington (C. R.), Biochem. J. (Lond.), 1924, 18, 85-92.

It is concluded that the increase in metabolism in exophthalmic goiter is due primarily to the acceleration of the endogenous oxidative processes, the increase in tissue breakdown being secondary to this effect. The results in myxedema are difficult of explanation. The theory developed from the observations leads to the idea that a low-protein diet is contra-indicated in hyperthyroidism. Acting on this assumption it was found that the basal metabolism tends to be lower on a rich protein diet and no ill effects obtained.—F. S. H.

Ovarian opotherapy and goiter (Opothérapie ovarienne et goitre). Coulaud (E.), *Ann. de méd. (Par.)*, 1923, 14, 517-534.

After reviewing briefly the literature concerned with the relation of the thyroid to the sexual cycle in women, the author reports a large series of cases in which goiter was treated by ingestion of ovarian products (dose from 0.2 to 0.4 gr. per day for 3 months). In 6 patients the results were negative; in 9 the circumference of the neck was not diminished but softening of the goiter occurred; in 59 the circumference of the neck was diminished from 1 to 3 centimeters; in 17 the diminution ranged from 3.5 to 7; and in 9 subjects the goiter disappeared. No other medication was employed. In the post-climacteric goitrous cases ovarian treatment was followed by loss of weight in those who showed a tendency toward adiposity. In those who had not reached the menopause the effect was not produced. It is therefore concluded that ovarian opotherapy is efficacious in the treatment of goiter and has no contra-indications. Administration of ovarian products over a long period of time produced no modification of the incretory glands of the rabbit.—F. S. H.

The influence of thyroid substance on the absorption of pleural effusions. Danzer (C. S.), *Proc. Soc. Exper. Biol. & Med. (N. Y.)*, 1924, 21, 298-301.

Three subjects with parapneumonic pleural effusion were treated with thyroid substances. The effusion was more rapidly absorbed than is usual. No results followed in a case of primary pleural effusion, probably tubercular.—J. C. D.

The relationship of goiter to mental disorders. Foss (H. L.) & Jackson (J. A.), *Am. J. M. Sc. (Phila.)*, 1924, 167, 724-735.

The close observation of about 800 goiter cases coming to a general hospital for treatment and the simultaneous study of 50 goiter patients among 1700 inmates of a large hospital for the insane, both institutions in the same locality and drawing their patients from the same territory, led Foss and Jackson to conclude that goiter is not, even in a goitrous district, especially common in the insane; rather the reverse, for its incidence in the State Hospital at Danville, Pa., is but 3%. Conversely, insanity is extremely rare among the large number of goiter patients applying for treatment in a general hospital in the same locality, there being no cases of true insanity among the 800 patients studied, the only mental disturbance being in the form of a mild excitement or rarely slight and transient mania, this in but 2 cases. There is, apparently, no definite relationship between goiter and insanity and surely nothing to indicate thyroidectomy in the treatment of the usual insane patient suffering from complicating goiter, unless for the relief of mechanical pressure. Operation, of course, may be indicated if there be accom-

panying evidences of true hyperthyroidism, but this latter condition is most rare. Neither hyperthyroidism nor hypothyroidism occurs, except very rarely, among the adult goiter patients of the Pennsylvania hospitals for the insane, the greatest number of goiters being of the so-called multiple adenomatous or nodular forms and unaccompanied by systemic disturbances.—R. G. H.

**Thyroid physiology in the frog** (*Contributo allo studio della fisiologia della tiroide della rana*). Gayda (T.), *Gior. d. r. Accad. di med.* (Torino), 1921, 4 s. 27, 405-407.

In the frog the thyroid seems to be important only when the organism is developing. In the adult thyroid extirpation or enteral or parenteral thyroid administration gives no notable results.

—P. M. N.

**Basal metabolism in office practice.** Haller (D. A.) & Clayton (M. M.), *J. Lab. & Clin. M.* (St. Louis), 1924, 9, 437-443.

This is a report of a series of observations to substantiate the opinion that basal metabolic determinations can be successfully made in the physician's office.—I. B.

**The effect of thyroid and parathyroid deficiency on the gross chemical composition of the long bones.** Hammett (F. S.), *J. Biol. Chem.* (Balt.), 1924, 59, xli.

When the thyroid apparatus is removed from albino rats 100 days of age a distortion of the course of differential development in gross chemical composition is exhibited. The nature of the disturbance consists of a combined partial desiccation and a retardation of ossification. When the parathyroids alone are removed there is no such change in the male; but in the female retardation of ossification is evident.—Author's Abst.

**The differential diagnosis between beginning or low-grade hyperthyroidism and the exhaustion of the body due to focal infections.** Hoxie (G. W.), *Med. Clin. N. Am.* (Phila.), 1924, 7, 1119-1126.

This is a report of 4 cases in which, because of the vague clinical pictures, the diagnosis was at first uncertain. Calorimetric tests are of great value in these borderline cases. Exhaustion of the resistance of the body such as may occur in the presence of focal infections may give rise to diminished sugar tolerance; this must not be hastily attributed to a primary endocrine disturbance.—I. B.

**The differential blood count in hypothyroidism.** Hutton (J. H.), *Illinois M. J.* (Oak Park), 1924, 45, 272-273.

Hutton believes that thyroid hyposecretion is associated with a reduction in the percentage of polynuclear leucocytes. In a study

of 29 cases presenting a basal metabolic rate of from minus 6 to minus 28%, the polynuclear count averaged 60%. The author concludes that there is a probable relationship between the percentage of polynuclears and the state of activity of the thyroid gland, and that this is related to the problems of immunity of the body to infections.—I. B.

**Exophthalmic goiter and involuntary nervous system.** Hyman (H. T.) & Kessel (L.), *Arch. Surg. (Chicago)*, 1924, 8, 149-165.

The course of subjective and objective manifestations in 50 unselected patients observed by Hyman and Kessel over a period of 2 years, in whom no specific therapeutic measures were instituted, is detailed. Apparently the spontaneous course of exophthalmic goiter is toward economic restitution in the majority of cases (83%). Recovery was not complete in the sense of cure, but was marked by the persistence of residual subjective symptoms. These residual symptoms did not interfere with economic restitution. In at least the first two years of remissions, severe incapacitating exacerbations were infrequent. These results of "skillful neglect" compare favorably with the results of specific therapeutic measures.—*J. Am. M. Ass.*, 82, 822.

**Hyperthyroidism complicating pregnancy.** Jackson (A. S.), *Ann. Clin. Med. (Balt.)*, 1924, 2, 303-311.

The occurrence of hyperthyroidism in pregnancy is increasing, due to the spread of goiter. The literature indicates that in the past a very conservative view has been maintained with regard to thyroidectomy in cases of goiter associated with pregnancy. The early diagnosis of toxic goiter (due largely to the recognition of the value of the basal metabolic rate), the perfection of teamwork in the operating room, and the discovery of the newer methods of treatment have been the means of reducing the operative mortality to a minimum. These advances should influence the obstetrician not to delay surgical intervention in the thyroid either in exophthalmic goiter or in frank cases of toxic adenoma. The necessity for therapeutic abortion is now of rare occurrence. Medical treatment is indicated only in mild cases of toxic adenoma or in incipient cases of exophthalmic goiter developing near the termination of pregnancy. Thyroidectomy in the two cases reported here proved as safe as in cases not associated with pregnancy.—Quoted from Original.

**Endemic goiter.** Keith (W. D.), *Canad. M. Ass. J. (Toronto)*, 1924, 14, 284-289.

This paper is a valuable study of goiter in the Pemberton Valley, B. C. (45 to 50 miles long, in the Coast Range, watered by the Lilloet River, fed directly from a glacier), based largely on the observations of John Ronayne, a large farmer in the valley and

mented and confirmed with histological examination of different thyroid material. At the end of 1917 many men, almost every woman, and every child born in the valley had goiter. Large litters of pigs were born, most of which were hairless and died within a day. Those with some hair which survived a few days became hopelessly myxedematous. In these the thyroid was larger than usual, dark red, and engorged with blood. All cows had some slight enlargement of the thyroid and gave birth to goitrous calves, of which few survived, and some of these were cretins. Many cows producing goitrous calves carried them a month over usual term. All mares became goitrous, and after being in the district 3 years their foals were goitrous. The second colts were carried 12 and sometimes 13 months, and were goitrous; few survived. These, 15% were carried only 11 to 11.5 months. The meconium in the colts that died was rubbery in consistency. The farm animals were more subject to goiter or exhibited it more in late winter and early spring. Chickens, ducks and turkeys brought into the valley appeared to thrive, but their eggs, though producing embryos, failed to hatch out, the apparent cause being thickening of the white envelope within the shell (which became rubbery). Marine's procedure of iodide administration was applied to animals and birds. In October, 1922, no goiter could be found in the valley. No wild animals killed in the district showed an enlarged thyroid. The district is virgin soil with a remarkably pure water supply. The disease was more pronounced higher up the valley. Poor sanitation existed only in the Indian village at the lower end of the valley; here no goiter occurred in human beings or pigs. Endemic goiter found under such conditions appears to be an iodine-deficiency disease. Iodine is now given only in winter and early spring. Some results were obtained suggesting that excess of iodine caused a lack of fecundity.

—A. T. C.

The chemical reactions involved in the physiological functioning of thyroxin. Kendall (E. C.), J. Biol. Chem. (Balt.), 1924; 50, xxxix.

During the synthetic work leading to the elaboration of thyroxin a derivative was produced which differed from thyroxin in having one more bond and two less hydrogens. Both of these forms occur in the thyroid gland. The function of the thyroxin is to regulate the capacity of the cell to use oxygen. The rate of this functioning depends on the physical state of the cell. The alternate oxidation and reduction is regulated by the opening and closing of the pyrrol ring in the tissues. This is in turn dependent upon the concentration of positive and negative charges present. It therefore appears that thyroxin makes any cell more sensitive to external—that is, physical—conditions.—F. S. H.

Toxic substances in the serum of thyroidless and parathyroidless animals studied by means of the respiratory exchange (*Beiträge zur Physiologie der Drüsen*. 58. Leon Asher. Prüfung der Frage von giftigen Stoffen im Serum schilddrüsenloser und parathyreopriver Tiere mit Hilfe des respiratorischen Grundumsatzes). Jino (K.), *Biochem. Ztschr.* (Berl.), 1924, 145, 105-115.

Rabbit serum when injected intraperitoneally into rats in amounts from 1 to 2 cc. raises the respiratory exchange slightly. The serum of completely thyroidectomized rabbits does the same, though to a lesser degree. This fact is evidence against the assumption of the presence of toxic substances in the blood sera of thyroidless animals. When serum from rabbits at the height of parathyroid tetany is injected into rats there is produced a marked lowering of the respiratory exchange.—F. S. H.

A review of another year's work with thyroid disease. Lahey (F. H.), *Boston M. & S. J.*, 1924, 190, 153-157.

The author concludes that thyroid extract is contraindicated in toxic cases and that prolonged iodine feeding may convert non-toxic into toxic goiter. Hyperthyroidism does not exist in the absence of increased basal metabolism rate and cures of hyperthyroidism are not accomplished without returns of basal metabolism rate to normal, provided there are no conditions other than a thyroidism elevating it. Basal metabolism readings are of great value in neuroses simulating thyroidism, in that the true basal metabolism rate in the neurosis is normal. Basal metabolism readings uncorrelated are not a reliable guide to the number or extent of operations a patient will stand. Minus degrees of basal metabolism rate may exist in patients free from clinical evidence of myxedema, yet made subjectively better by raising the rate to normal with thyroid feeding. Multiple stage measures are life-saving procedures in severe hyperthyroidism. Thyro-cardiac cases first seen in decompensation may be restored to striking cardiac capacity if it is possible by thyroidectomy to remove the intoxication and to restore the heart rate to within normal limits. The most dreaded, uncertain and uncontrollable factor in the author's clinic today is mediastinitis. The moderate values of x-ray treatment are more than outweighed by its disadvantages. Thyroid surgery done in a general surgical clinic equipped for the care and study of these subjects will show few failures to cure and a mortality rate rarely over and in most cases under 1%.—J. C. D.

Basal metabolic rates in some of the psychoneuroses. Levine (B. S.), *J. Lab. & Clin. M.* (St. Louis), 1923, 8, 775-789.

This report is based upon basal metabolic determinations carried out in 100 cases presenting two or more cardinal signs of hyperthyroidism. The primary complaint in all patients was nervousness.



tion of the thyroid gland, fasting, thyroid feeding, withholding of the water-soluble vitamins from the diet, inhalation of oxygen, nitrogen, hydrogen or carbon dioxide gas, administration of atropine, pilocarpine, adrenalin, potassium arsenite or hydrogen cyanide. Normal control animals were observed at intervals over a period of 4 months to have no changes in the mitochondria. At intervals of a few days individual animals in the various series were examined with regard to the mitochondrial changes in the thyroid cells. All thyroid tissue was first fixed in the following mixture devised by Pianese: 1% aqueous solution of sodium platinic chloride, 15 cc.;  $\frac{1}{4}$ % aqueous solution chromic acid, 5 cc.; 2% aqueous solution osmic acid, 5 cc.; formic acid C. P., 1 drop. The gland was then examined in section for mitochondria. Fragmentation of mitochondrial filaments into granules was found to follow most of the above procedures. Reduction in the number of mitochondria was observed coincidentally with this change. The number of mitochondria was increased in the cases with compensatory thyroid hypertrophy following removal of some three-fourths of the thyroid tissue.—I. M.

**Operative results of thyroidectomy and thymectomy in the rabbit.**

Pearce (Louise) & Van Allen (C. M.), *Proc. Soc. Exper. Biol. & Med.* (N. Y.), 1924, **21**, 319-320.

This is a report on the operative mortality. Thymectomy does not affect the animals while thyroidectomy results in lowered resistance to various things including syphilis and transplantable malignant tumors.—J. C. D.

**Goiter survey in Wexford County, Michigan.** *Pub. Health Rep.* (Wash.), 1924, **39**, 663-664.

Of the total number of boys and girls examined, 2247 were in the city of Cadillac, where thyroid enlargement was found to be present in 50.4%. Of the boys examined in Cadillac, 41.8% were found to have thyroid enlargement; and of the girls, 58.0%. In the rural and village schools of Wexford County outside of Cadillac, 62.2% of the children were found with thyroid enlargement—54.2% of the boys and 71.0% of the girls. The water supply of the city of Cadillac shows a very slight trace of iodine, whereas no iodine is found in the water in the rural districts of the county. The average city dweller probably has more opportunities to secure iodine in his food supply than has the rural dweller, on account of his somewhat more varied diet. Sea foods, ordinarily only infrequently supplied to rural districts, are more common in the markets of the city. Another possible factor mentioned is that medical treatment is more generally available in the city than in the country.—R. G. H.

**Comparison of the oxygen consumption of surviving organs of mammals in the normal condition and after feeding with thyroid (Bei-**

träge zur Physiologie der Drüsen. 61. L. Asher. Vergleich des Sauerstoffverbrauches überlebender Säugetierorgane im normalen Zustande und nach Fütterung mit Schilddrüsenhormon). Rohrer (A.), Biochem. Ztschr. (Berl.), 1924, 145, 154-167.

The liver, kidney, and muscle tissues of mice were used in these studies. It was found that previous feeding of the animals with thyroid preparations enhanced the oxygen consumption of the surviving organs.—F. S. H.

The Kottmann reaction in the insane. Saunders (A. M.), J. Lab. & Clin. M. (St. Louis), 1924, 9, 401-403.

The author finds the Kottmann test of greater value than basal metabolism determinations in the diagnosis of thyroid disturbances in the insane.—I. B.

Kottmann's photo-reaction as evidence of thyroid function (Beiträge zur klinischen Konstitutionspathologie. X. Zur Bewertung der Kottmannschen "Photoreaktion" als Funktionsprüfung der Schilddrüse). Schur (M.), Ztschr. f. Konstit. (Berl.), 1923, 9, 412.

After testing 8 patients with exophthalmic goiter, 3 with myxedema and 1 imbecile with hypothyroidism, Schur concluded that Kottmann's photo-reaction (1 cc. fresh serum plus 0.25 cc. 0.5% potassium iodide and 0.3 cc. 0.5% silver nitrate solution, exposed to the light and developed with 0.5 cc. 0.25% hydrochinon) is not a reliable indicator of thyroid activity.—A. T. R.

Immediate effect of subtotal thyroidectomy in toxic goiter. Segall (H. N.) & Means (J. H.), Arch. Surg. (Chicago), 1924, 8, 176-188.

It is generally recognized that the clinical improvement following successful subtotal thyroidectomy is a relatively rapid one. Segall and Means express this improvement precisely by means of daily basal metabolism and pulse rate curves, and thus show the actual rate of detoxication in quantitative terms. From the studies reported, it is concluded that the rate of detoxication following subtotal thyroidectomy is quite similar to that during recovery from hyperthyroidism induced by thyroid feeding. The time required for detoxication depends on the intensity of the preoperative intoxication. While pulse and basal metabolism show considerable parallelism, the latter fluctuates less and is the better index of the degree of hyperthyroidism. The slight rise in pulse and metabolism which is usual just before operation is due to emotional tension, and very likely a resulting increase in liberation of epinephrin.

—J. Am. M. Ass., 82, 822.

**Congenital goiter.** Skinner (H. H.), J. Am. M. Ass. (Chicago), 1924, 82, 1190-1192.

Twelve cases are reported. The author concludes that congenital goiters are more common than it has been ordinarily supposed. They are caused by iodine deficiency in the mother's diet. All grades of pathologic change may be seen, from a simple parenchymatous goiter with no symptoms, to marked enlargement with complete tracheal compression and cystic conditions causing serious danger to mother and child. Treatment is surgical for emergencies, but mainly prophylactic by means of iodine administration to the mother.—R. G. H.

**The effect of treatment in hyperthyroidism controlled by observations of the basal metabolic rate.** Trumble (H. C.), Med. J. Australia (Sydney), 1924, i, 131-135 (Suppl.).

Trumble reports a number of cases of exophthalmic goiter and toxic adenoma (not differentiated) divided in 4 groups as follows: Group I—Two cases treated by half-hearted medical measures, such as the hospital out-patient department treatment. Group II—Seven cases receiving careful medical treatment, with prolonged rest in bed. Group III—Five treated by exposure to x-rays. Group IV—Twelve subjected to operation. He concludes that exophthalmic goiter and toxic adenoma of the thyroid gland are diseases which tend to progress to the detriment of all tissues of the body; the heart and nervous system suffer more especially. The most effective measures at present available in the treatment of these cases are rest, x-rays and partial thyroidectomy. Rest is but rarely sufficient, though generally followed by slight improvement. Treatment by x-rays in this series was not generally successful, but in certain cases is probably of great use. Removal of one lobe is usually followed by great improvement, but recurrence of symptoms appears to be common. Radical removal of two-thirds to five-sixths of the gland offers the best chance of cure at present available.

—R. G. H.

# Endocrinology

## *The Bulletin of the* *Association for the Study of* **Internal Secretions**

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### RECENT WORK ON INSULIN \*

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#### INTRODUCTION

The discovery of insulin, which was reported some two years and a half ago, has been followed by publications from an extremely large number of investigators. It is interesting to note that many groups of workers have reported several times on this subject. It is quite obvious, therefore, that insulin is an interesting theme which is not easily exhausted. The large amount of literature which has accumulated makes it necessary to limit our discussion today to certain phases of the recent developments. It will be advantageous to dwell more particularly upon those aspects of insulin in which our laboratory is especially interested and which, at the present time, we are actively investigating. This will give me the opportunity of submitting to you the results of our recent experiments, as well as to review some of the published work of other observers. I shall try to touch upon phases of insulin other than those which have been very completely discussed in recent reviews.

#### THE PREPARATION OF INSULIN

The comparatively simple method for the preparation of insulin as originally published from Toronto (1) has been fol-

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\* Read at the Eighth Annual Session of the Association for the Study of Internal Secretions, Chicago, June 9, 1924.

lowed by the report of many modifications and improvements. At least twelve groups of observers have already reported on this aspect of the subject. I will not attempt to discuss the details of all the various methods, but you may be interested to hear in a general way of our experience with certain significant new developments.

The first solutions of insulin were made by watery extraction of pancreas. Alcohol was introduced as a solvent by the original investigators (2) and has remained the most popular extractive up to the present time. This solvent has been used continuously in Toronto in the routine preparation of material for clinical use, with the exception of a few months in the spring of 1922 when acetone was employed. Doisy, Somogyi and Shaffer (3) have used alcohol as the extractive in their method. These investigators introduced the precipitation of insulin from watery solution by half saturation of ammonium sulphate, and, coincident with Walden of the Eli Lilly and Company, the isoelectric method of purification. Fisher (4) has slightly modified this method by employing a higher concentration of alcohol than used by the previous investigators to fractionally precipitate the inert protein material. He claims to eliminate by this procedure a larger amount of those substances in the pancreas which antagonize the action of insulin. The existence of these substances was recognized very early in the work on insulin. Dudley (5) has retained the alcoholic extraction of the earlier methods as the first stage of his procedure for the preparation of insulin and has developed the so-called picric acid method of purification. In this method insulin is precipitated from watery solution, as the picrate, by the addition of picric acid. The picrate is subsequently treated with hydrochloric acid in 75 per cent alcohol and insulin is liberated as the hydrochloride. The hydrochloride is precipitated from alcoholic solution by the addition of ether or acetone. This method has been extensively used by manufacturers in England. Dudley (6) has recently published certain modifications of his method. He has obtained very satisfactory results by using alkaline alcohol as the extractive. Krogh (7), of Copenhagen, uses alcohol as the extractive. He believes that improved results are obtained when the glands are frozen as soon as possible after collection. The frozen mate-

rial is subsequently minced into acid alcohol. Robertson and Anderson (8) use alcohol as the extractive. They advocate the addition of sodium sulphate as a dehydrating agent, to the alcoholic filtrate from the glands. Moloney and Findlay (9) have recently published a second method based on the sorption of insulin. Charcoal is used as the sorper in this method.

Several groups of observers believe that water is a satisfactory extractive for insulin. Murlin (10) and his collaborators have used both alcohol and water as extractives. Using the latter, they have compared the yields of insulin obtained from the pancreas by perfusion, percolation and simple extraction. The fact that perfusion yielded the greatest amounts of insulin is of physiological interest. Dodds and Dickens (11) have reported the successful use of aqueous formic acid (1 per cent) as an extractive for insulin. These workers applied Dudley's method for the purification of the product. Very recently Dodds and Dickens (12) have reported favorable results with certain procedures which differ very considerably from their original method. The aqueous extraction is abandoned and extraction with acetone of glands which have been thoroughly minced and mixed with powdered picric acid, is substituted. We have been unable thus far to secure any better results with any of the above-mentioned methods than with the acid alcohol extraction method which we have used for the past half year for the preparation of material for clinical use. This method is essentially similar to that described by Scott and the writer (13). Detailed reference to the methods used in Toronto is given in this article. We find alcohol very strongly acidified with sulphuric acid, the most satisfactory extractive. The use of strong acid at this stage is advised by Somogyi, Doisy and Shaffer (14). In the search for better methods for the preparation of insulin many new properties of the substance have been discovered. This will undoubtedly result in the eventual development of very economical methods of production.

#### THE PROBLEM OF TESTING

Several methods of testing insulin are in use. The rabbit method is used by the Insulin Committee of the University of Toronto. A formula which facilitates the calculation of the potency in units per cubic centimeter is used. This method was

reported at the 1923 Meeting of the American Physiological Society by Orr of the Insulin Committee testing staff. The Unit as defined by the Committee is one-third the amount of insulin necessary to lower the blood sugar of a 2000-gm. rabbit, which has been starved 24 hours from the normal level to 0.045 per cent over a period of five hours. In our research work, whenever there is an ample supply of insulin-containing extract, we determine roughly the smallest amount of material necessary to lower the blood sugar of a 2000-gm. rabbit to about 0.060 per cent—that is, an amount which will produce an appreciable effect but not cause convulsions. We then administer a series of doses grouped closely about this roughly determined minimum dose to a number (6-10) of carefully selected rabbits. The rabbits are either absolutely fresh or have had at least a week of rest from use as test objects. The blood sugar is determined before and 1½, 3 and 5 hours after the injection of insulin. The unitage is calculated from the formula. The results are averaged and this value is taken as the unitage of the solution being tested. In testing a lot which is to be used in the clinic, from twenty to thirty rabbits are used.

The British Medical Research Council have used mice as test objects. Fraser (15), of the Connaught Laboratories, has published a method in which mice are used. The minimum dose required to produce typical convulsions is determined. Krogh, of Copenhagen, uses mice which are kept under standardized conditions such as temperature and diet. Although good results are claimed by individual investigators, difficulties have been experienced in co-relating the results of the different workers. Voegtlin, Dunn and Thompson (16) state that they have developed a reliable method for the standardization of insulin. The method is based on the lethal effect produced by insulin on “standardized albino rats kept under standard conditions of diet and atmospheric temperature.” F. N. Allen (17) Department of Physiology, University of Toronto, has carefully determined the glucose equivalent of insulin on depancreatized dogs. The glucose equivalent was found to become progressively smaller as the dose was increased. Work of this type may provide us with an accurate method of assaying insulin. Finally, the clinical method of assay in the hands of expert clinicians

working on "pedigreed" patients has yielded fairly consistent results. Clinicians have detected variations of two or three units in potency. On the other hand, however, on certain occasions they have believed that they noticed a variation in the insulin when no variation existed. The difference was probably due to some changes in the clinical condition of the patient, of a nature too subtle to produce signs or symptoms. Nevertheless, the clinicians are the judges of our laboratory methods of standardization, and when our technique is good enough to produce lots so uniform in potency that they cannot distinguish between them there will be little cause for worry.

The Medical Research Council of Great Britain is engaged in preparing a stable insulin hydrochloride which after standardization may serve as the official standard.

#### YIELDS OF INSULIN

There are great variations in the findings of those investigators who have reported on the yields of insulin from pancreas. The variation is due partly to differences in the methods of testing, partly to the varying degrees of purity of the material under test, and only partly to the amount of insulin extracted from the gland by the method. It is impossible to evaluate a method when little or nothing is reported concerning the first two factors. Dodds and Dickens (18) report a yield of crude insulin of approximately 5500 clinical units per kilogram of pancreas. Moloney and Findlay (9) report the demonstration of 4400 units per kilogram of pancreas. Clough, Allen and Murlin (19) publish results demonstrating over 4500 units of crude insulin per kilogram. Dudley and Starling (20) obtain a maximum yield of about 1500 units of insulin, as finished hydrochloride, from one kilo of ox pancreas. Acid alcohol as used in our method extracts from 1500 to 2200 units per kilogram of pancreas. Consistent yields of 1100-1200 units of purified material (nitrogen 0.006 mgm. per unit) are obtained. In view of the variation in reported yields of insulin from pancreas, the matter might be simplified if the yield were always stated in terms of units of a finished product which has been found to be completely satisfactory in the clinic.



## THE DISTRIBUTION OF INSULIN

In the search for the antidiabetic principle the pancreas has not been the only tissue investigated. The work of those who sought for this substance in blood will be familiar to you. Hédon (21), Hess, Forsbach, Alexander and Ehrmann, Drennan, Kramer and Murlin and others have studied the effects of transfusing diabetic animals with normal blood. Clark (22) has reported very significant results obtained by passing pancreatic perfusate through the isolated mammalian heart. Woodyatt and Raulston (23) were unable to observe any beneficial effect of the transfusion of normal blood to a severely diabetic patient. The recent work of Murlin (24) and his collaborators has been previously referred to in this communication. It should be noted that unsuccessful perfusion experiments have been recently reported by McCarthy and Olmstead (25) and that several groups of investigators have previously reported negative results with this method. There is no doubt, however, that this method has yielded very successful results in the hands of Clough, Allen and Murlin.

The method originally used for the preparation of insulin from the degenerated pancreas of the dog was not sufficiently delicate to demonstrate active material, in a convincing manner, in other tissues. The isolation of insulin from blood was reported from Toronto in May, 1923 (26). This, I believe, was the first report of the presence of insulin in tissues other than the pancreas. In Table I the report of an experiment in which an extract of blood was administered to a diabetic dog is summarized.

## EFFECT OF BLOOD EXTRACT ON THE DIABETIC DOG

*Dog. No. 18.* Brown collie. Weight 14 kilos. Pancreatectomy performed September 17, 9 p. m. Dog was then starved.

The marked and characteristic response of this animal to the extract is convincing proof, in my opinion, of the presence of insulin in blood. You will note that a marked improvement in the general condition of the animal was observed, and that the liver, at autopsy, contained 5.85 per cent of glycogen. The typical insulin effect upon the blood and urinary sugar was

TABLE I

Date	Time	Blood Sugar %	Urine Vol.	Total N	Glucose Excretion	G Ratio N	Injections	Diet	Remarks
Sept. 19	9.00 a.m.	0.236%	355 cc.	11.0 gms.	34.1 gms.	3.1	3 cc. sterile blood extract.	Starved.	Animal very weak. Conjunctivitis both eyes.
Sept. 20	9.00 a.m.	0.220%	355 cc.	9.9 gms.	32.1 gms.	3.2		Starved.	
Sept. 21	11.20 a.m.	0.260%							
	1.50 p.m.	0.268%					4 cc. blood extract (Intrav.).		
	4.20 p.m.	0.256%					5 cc. blood extract (Subcut.).		
	4.30 p.m.	0.205%					15 cc. blood extract (Intrav.).		Animal in excellent condition. Eyes much improved
	6.30 p.m.	0.250%					4 cc. urine extract, No. 261.		
Sept. 22	9.00 a.m.	0.224%	380 cc.	9 gms.	31.7 gms.	3.2	3 cc. blood extract washings.		
	10.00 a.m.	0.230%					4 cc. blood extract washings.		
	11.30 a.m.	0.224%					5 cc. blood extract washings.		
	2.00 p.m.	0.224%							Animal in excellent condition. Eyes much improved
Sept. 23	3.30 p.m.	0.274%	190 cc.	5.8 gms.	17.9 gms.	3.1	2 cc. blood extract washings.		
Sept. 24	9.00 a.m.	0.148%	375 cc.	10.9 gms.	41.4 gms.	3.8	4 cc. blood extract washings.		
	2.00 p.m.	0.180%					5 cc. blood extract washings.		
	7.00 p.m.	0.218%							
Sept. 25	11.00 p.m.	0.167%	135 cc.	4.9 gms.	5.8 gms.	1.2			Animal in excellent condition. Eyes much improved
	9.00 a.m.	0.079%					2 cc. blood extract washings.	50 cc. weak insulin sol. stomach tube.	
	11.30 a.m.	0.048%					4 cc. blood extract washings.	10 gms. glucose, stomach tube.	
	4.30 p.m.	0.085%						¼ lb. beef.	
	8.00 p.m.	0.085%						50 gms. glucose, ¼ lb. meat.	
Sept. 26	12.00 p.m.	0.136%	185 cc.	6.5 gms.	Neg.	—		¼ lb. meat.	Animal in excellent condition. Eyes much improved
	9.00 a.m.						2.5 cc. blood washing.	50 gms. glucose, stomach tube.	
	9.30 a.m.						6.0 cc. blood extract washing.	¼ lb. meat.	
	10.30 a.m.	0.051%					50 gms. glucose (Intrav.).		
	11.30 a.m.	0.145%							
Sept. 27	9.30 p.m.	0.104%	350 cc.	6.3 gms.	Neg.	—			Animal in excellent condition. Eyes much improved
	9.00 a.m.								
	9.30 a.m.								
	10.00 a.m.								
	11.30 a.m.	0.060%							
	4.00 p.m.	0.060%							Animal in excellent condition. Eyes much improved
	5.30 p.m.	0.085%							

Animal killed 6.00 p.m., September 27th. The liver contained 5.85% glycogen and 12.76% fatty acids.

produced.\* This extract was also administered to a number of normal rabbits. Characteristic insulin convulsions, which were permanently alleviated by dextrose, were produced when the dose was sufficient to cause marked hypoglycemia. A substance which consistently produces all these effects possesses the essential and characteristic properties of insulin.

Scott, Smith and I (27) have reported in detail on the presence of insulin in practically all the tissues of the body. We found insulin in the tissues of completely depancreatized dogs. Some of these animals were in the end stages of diabetes when they came to autopsy. Ashby (28) has been able to extract insulin from various tissues. He was not able to demonstrate any antidiabetic substance in diabetic tissues. Several European investigators have recently reported the presence of insulin in various organs. Very recently Vincent (29) reports that Dodds and Dickens have applied their revised method to the extraction of insulin from ox submaxillary gland and that a yield of 2130 units per kilogram has been obtained. Vincent states that "the fact that such large quantities can be prepared from a gland so like the pancreas in general structure cannot be without some fundamental significance. McAlpine in our laboratory has thus far been unable to secure yields from this source comparable to those reported by Vincent. McAlpine has used the revised Dodds and Dickens method. The significance of this active material in tissues other than pancreas is not increased in proportion to the absolute amount extracted by a certain method but depends more upon (1) the demonstration that the substance is insulin, and (2) the amount extracted by a given method compared to the amount extracted from the pancreas by the same technique. As we have reported elsewhere, thymus glands processed by our present methods are a much more fruitful source of insulin than pancreas extracted by the procedure originally used to prepare insulin for clinical use. The fact that the pancreas is far richer in insulin than any other tissue should not be overlooked.

There is still much to be learned concerning the distribution of insulin in the body, but I believe that we should await developments in methods of preparation and especially of testing

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\* A weak insulin solution, as noted in the table, was administered *per os* to this animal by mistake. A large amount of the potency was recovered from the urine. Numerous control experiments show that insulin *per os* does not affect the blood sugar or liver glycogen.

before a complete study which will necessarily require much time and expense is undertaken.

The exact significance of insulin in diabetic tissues is not known at present. We have made the obvious suggestion that the insulin must be present in a comparatively unavailable form. This is the only explanation, unless the generally accepted conception of the significance of the persistently low respiratory quotient in diabetic animals is doubted.

We have recently attempted to analyze the tissues of dogs thoroughly poisoned with phloridzin. Very little can be stated concerning these results as yet, but it appears that insulin is present in normal amounts in the pancreas and in demonstrable amounts, at least, in other tissues.

The bearing these results will have on the islets of Langerhans theory of diabetes remains to be determined. Although the great mass of pathological and physiological evidence supports this theory it has been vigorously attacked recently by Oertel (30) and by Vincent (31). These writers review work, mainly pathological, which leads them to the conclusion that the islets are not separate and distinct structures but are temporarily modified portions of the secretory tubules of the pancreas.

#### THE INSULIN-LIKE MATERIAL IN PLANTS

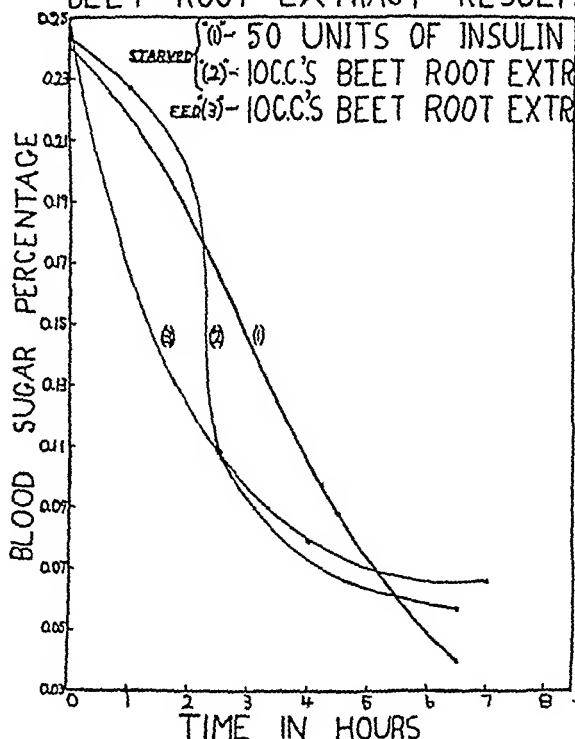
The literature dealing with the insulin-like material in plants has been briefly reviewed elsewhere (32). Macleod (33) points out that care should be exercised in considering these results since hypoglycemia may be caused by certain chemicals, by lowered blood pressure, by injury to the liver, or by stimulation of the pancreas. Stress has been laid on the delayed action of vegetable extracts by Collip and others. We submit curves showing the relative speed of action of a purified sample of vegetable extract as compared to that of an average dose of pancreatic insulin. In each of the three experiments the blood sugar had returned to its previous level by twelve hours after the time of the last determination shown on the chart.

You will observe that the beetroot extract exerts its effects on blood sugar as rapidly as insulin. The latter part of the experiment was conducted in the same manner as the early experiments by the Toronto group (34) when the effect of insulin on glycogen formation in diabetic dogs was being studied.

This diabetic animal was given large quantities of dextrose and beetroot extract. The liver at autopsy contained over 9 per cent glycogen. No pancreatic tissue was found. As our knowledge of the properties of this purified plant extract increases the similarity between it and pancreatic insulin becomes more marked. The yields of this active material from plants are very small

TABLE II

## BEET ROOT EXTRACT RESULTS



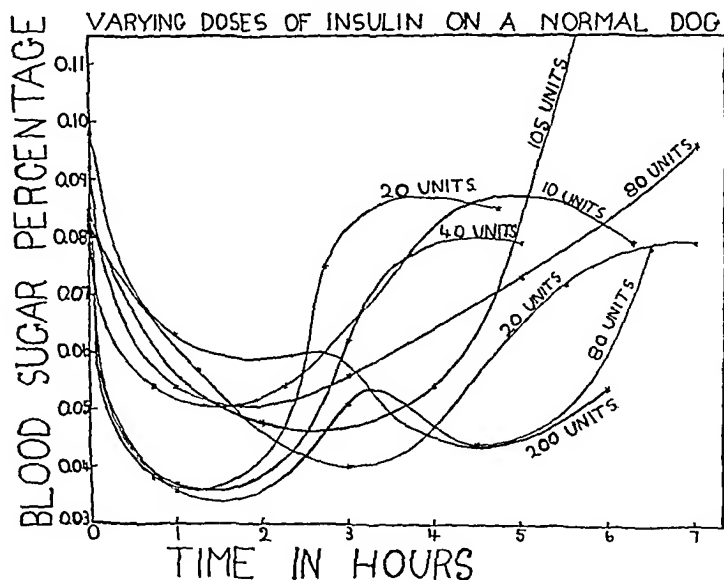
and the raw material is processed with much greater difficulty than is pancreas. The peculiar animal transfer phenomenon noted by Collip (35) remains as yet unexplained.

## THE EFFECTS OF LARGE DOSES OF INSULIN ON DOGS

It has become apparent to many of those who have used rabbits extensively in testing insulin that a large dose does not invariably produce a greater effect upon an animal than a much smaller amount. This effect appears to be independent of the glycogen store of the animal at the time of the experiment. The work of F. N. Allen on dogs is interesting in this connection and has been referred to previously. Smith and I are engaged in a

study of the effect of large doses of insulin on dogs. As this work is by no means completed, I will present our results only very briefly. In Table III the effects of varying doses of insulin upon a normal dog are shown. This animal had approximately one week's rest between each two experiments. The animal was on a constant diet for several weeks before and during the experiments. The insulin was injected at the same time of day in each experiment. A study of the chart reveals the irregular nature

TABLE III



of the results. In some, but not in all experiments, we have noted a definite increase in the insulin content of the urine after large intravenous doses of insulin. In one experiment an animal was killed some four hours after a very large dose. Various tissues were extracted and the extract tested on rabbits. A definite increase in the insulin content of the kidney was found, but other tissues contained only normal amounts. However, it seems probable that insulin may be stored in the body since an animal may apparently completely recover from the effects but at a subsequent time exhibit hypoglycemia and convulsions. An animal occasionally exhibits this temporary recovery when dextrose is not administered. We hope that further work will

throw light on the interesting problems which arise from these preliminary experiments.

I am indebted to Miss J. Ridout, M. A., for her efficient assistance in connection with some of the experiments referred to in this communication.

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#### (DISCUSSION OF PAPER OF DR. BEST)

Dr. John R. Murlin, Rochester, N. Y.: Dr. Best referred to our experiments in extracting insulin by perfusion and percolation. He said we obtained a greater yield by perfusion than by the other methods. That was true until we found an improved method of simple extraction which we think is better, and which we reported in our last article. We now obtain more insulin by the simple aqueous extraction, using hydrochloric acid and heat, than we do from the same pancreas by either percolation or perfusion. The amount runs as high as 5400 units per kg. of pancreas. However, our comparison has been made only on the crude extracts. We have not given any figures on the yield of insulin in the refined form. The reason for this is that, as reported last winter in St. Louis, we have found a

form of insulin which seems to be entirely free from protein. Until our study of this product is completed we do not wish to say anything about the yield of insulin in a refined form.

In the experiments which I have reported today we used this crude form of insulin.

In brief the method which we have used since early last year is as follows: We make our extracts with heat, using about 1/5 normal hydrochloric acid and heating to about 75 or 80 degrees C. It does not seem to make any difference whether one heats just to that point or maintains the heat for 15 minutes or longer up to one-half hour. After cooling and stirring the material we neutralize to a pH of about 4. This neutralization throws down a heavy precipitate and gives a clear straw-colored filtrate. Re-extraction of this precipitate, however, gives a much larger yield. Combining the filtrates we next precipitate with sodium chloride, and it is this salt precipitate dried which we have used in most of the tests on oral administration. The salt precipitate usually gives about 3 clinical units per 100 mgs. dry. If we wish to use a stronger dosage we make a much more potent dry product by dissolving the salt precipitate in 70% alcohol, distilling off the alcohol and redissolving in 80% alcohol. This leaves behind the salt. After two or three such treatments every trace of salt is removed. From the final 80% alcohol solution we precipitate with 3 to 5 volumes of amyl alcohol. This precipitate when dry will keep indefinitely and retain its potency and it contains approximately one unit per mg. Of course it is not free from protein.

Some of the tablets which we have used in oral administration have been made by combining some of the amyl alcohol precipitate with the salt precipitate, thereby increasing the potency of the latter without materially increasing the weight. All our endeavor along this line has been to cheapen the production of insulin if possible, and to get it into form which may be administered by mouth.



# THE CLINICAL ASSAYING OF INSULIN AND THE INSULIN REQUIREMENT \*

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In a publication which appeared in the *Insulin* number of the *Journal of Metabolic Research*, I, with Boothby and others, proposed a clinical method for assaying insulin. Properly selected patients were placed on a standardized maintenance diet high enough in carbohydrate to cause slight glycosuria, and a value for the tolerance under these conditions was reached by subtracting the average daily glucose excretion from the glucose value of the foodstuffs metabolizing. The diet was then increased to a glucose value of 100 to 120 gm., and insulin (Eli Lilly Company) was administered in amounts such that glycosuria continued in about the same degree. The extra grams of glucose metabolized under these conditions divided by the number of units of insulin gave a glucose equivalent for different allotments with an average value of 1.5 gm. and extreme variations of 0.9 to 3.1 gm. While these considerable fluctuations were noted with different lots of insulin, the results with the same lot were fairly uniform in different patients. In the same number of the journal Woodyatt proposed a similar procedure and reached similar conclusions, namely, that with properly selected patients each unit of insulin injected subcutaneously provided an increased tolerance of from 1 to 1.5 gm. sugar. During the succeeding year careful tests were conducted in the Mayo Clinic on a large number of later lots of insulin (Eli Lilly Company) with more consistent results than we had previously obtained (Table 1).

In October, 1923, the strength of the insulin Lilly unit was increased, but since then we have not conducted a sufficient number of useful assays to permit an accurate comparison between the present unit and the previous one. From our less exact

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\* Read before the Association for the Study of Internal Secretions, Chicago, June 9, 1924.

observations, however, the present unit apparently has a value of about 2 gm.

The supposition that a quantitative relationship exists between insulin and glucose is supported by the experiments on animals by Frank N. Allan of Toronto, who used two totally depancreated dogs that were excreting sugar and obtained fairly constant results when constant experimental conditions were maintained. Furthermore, the glucose equivalent of insulin varied with the dose in an orderly manner which could be ex-

TABLE 1  
CLINICAL ASSAYS OF INSULIN

Date 1923	Lot Number*	Assay	Date 1923	Lot Number*	Assay
Jan. 21.....	725737	1.6	Mar. 18.....	B 1460	1.3
24.....	725721	1.2	19.....	729780	1.7
26.....	725732	1.8	30.....	729777	1.9
27.....	725737	1.6	April 1.....	B 1464	1.7
Feb. 1.....	725745	1.7	5.....	B 1466	1.5
2.....	725740	1.6	13.....	729781	2.1
9.....	B 1438	1.3	13.....	729789	1.5
10.....	729748	1.9	15.....	B 1475	2.0
10.....	B 1439	1.6	15.....	B 1476	1.8
17.....	729748	1.9	26.....	733903	1.8
17.....	B 1440	1.6	26.....	729792	1.5
17.....	729752	1.2	28.....	733903	1.8
21.....	B 1442	1.2	30.....	B 1484	1.5
22.....	729753	1.9	June 1.....	B 1502	1.1
22.....	729752	1.2	21.....	B 1504	1.5
Mar. 3.....	729758	2.0	July 1.....	B 1514	1.5
5.....	B 1447	1.5	20.....	B 1521	1.7
10.....	729768	2.0	Aug. 1.....	B 1523	1.7
10.....	729759	1.2	16.....	B 1535	1.6
11.....	B 1450	2.0	27.....	B 1545	1.7
16.....	729775	2.0			
16.....	729774	1.5			
			General Average.....		1.65

\* The lots prefixed with a "B" are lots sent to us by the Eli Lilly Company for testing clinically. The strength of these lots had previously been determined by physiologic assays conducted on rabbits. The lots with six-figure numbers were those distributed for clinical use after preliminary testing in various hospitals.

In September, 1923, an arbitrary revision was made by the Eli Lilly Company and the strength of their clinical unit was increased 40%. Since that time the glucose equivalent of the unit has been regarded as 2 gm.

pressed by an equation, although when the dose was constant the glucose equivalent increased with carbohydrate increments. Allan's conclusions that the level of the carbohydrate balance must be taken into consideration in judging the glucose equivalent of insulin clinically, is probably correct, but his assumption that we failed to do this is unjustified. All of our patients were essentially on the same carbohydrate balance and such fluctuations as were found in our early series of experiments can, I believe, be satisfactorily explained by the inconstancy in strength

of the different lots of insulin available during that early experimental period. Subsequently, as stated, the various allotments have behaved with much greater uniformity. We have yet to encounter such high glucose equivalents for patients as Allan reports for the depancreated dog, namely, 4 to 6 gm. of sugar for each insulin unit, but the condition of the two sets of experiments are not the same, and the fact that fairly uniform results were obtained both by Allan's method and ours is of greater significance than the disagreement as to the exact value of the glucose equivalent.

The subject is of some importance since it bears directly on the problem of how insulin acts. If a given quantum of insulin will always accomplish the metabolism of a definite quantum of sugar under fixed experimental conditions, the presumption is strengthened that the action of insulin is directly on the sugar. On the other hand, the absence of any rhyme or reason in the action of insulin would be evidence opposed to such an assumption.

The patients on our service receive diets that are closely adjusted to their energy requirements, and these diets are proportioned so as to contain relatively little carbohydrate and protein. With other regimes it is probable that the effect of insulin will be greater or less than we find it to be, and this indeed has been the experience of Allen and Sherrill. Furthermore, the presence of complications may have a very considerable influence on the glucose equivalent of insulin, as will be discussed.

Allen and Sherrill contend, if my interpretation is correct, that insulin not only favors the metabolism of glucose, but that of other foodstuffs. In other words, increased food calories of any kind, according to their experience, increase the demand for insulin, the effect of fat on the insulin requirement being more delayed than that of carbohydrate, so that it may be overlooked in short period observations. The chief objection to this conclusion is that it is based on the observation of patients who were for the most part emaciated and receiving very small diets. It must be admitted that patients who are underweight and receiving starvation diets can be given larger doses of carbohydrate than will be tolerated by the same patients after they regain weight, or when they receive adequate calories; also that small

doses of insulin appear to exert a surprisingly great influence on starved patients. I cannot believe, however, that the metabolic processes of such patients are directly comparable to those of normally nourished persons, and before attributing such profound effects as those observed to the often minute doses of insulin employed in their treatment I should like to be more certain how much of the effect observed is attributable to starvation. Joslin, for instance, infers that a false value may be ascribed to the insulin unit in undernourished patients, who, he says, are like his Mr. P. in Case 866, who was 50 per cent underweight, and had been undernourished so long that it required about three weeks to develop glycosuria, although the diet was considerably enlarged. Had this patient received 1 unit of insulin a marvelous effect would have been attributed to the unit. Furthermore, a number of patients with diabetes have been observed in whom protracted starvation had caused hypoglycemia, and in some of these carbohydrate, which was administered as a restorative, disappeared from the blood as effectively as if insulin had been injected. Our experience has been that fat may be added to the diets of well-nourished diabetic patients without appreciably increasing the insulin requirement. While we do not advocate excessive diets, nearly all of our patients are receiving high fat diets which amply provide them with calories for work. For farmers, the diets often total 2700 calories, and such diets have now been continued, in many instances, for more than a year and a half, yet the doses of insulin required by these patients are not in excess of those Allen and Sherrill are using, and the insulin requirement in most cases has remained stationary.

Heavy protein feeding is supposed to exert a deleterious effect on diabetes, and should therefore increase the demand for insulin. Petrén, in particular, opposes large protein allowances for diabetic patients, and Newberg and Marsh attribute the success of their high fat regime to its low protein content. In part the action of protein may be explained by its cumulative effect on the basal metabolism, as seemed to be evident in our severe case, Bessie B. During high protein periods the basal metabolism of this patient was increased 20 to 30 per cent, and the depressant action on tolerance was extreme and considerably

greater than that of isocaloric and isosaccharine diets low in protein. Protein, however, appears to have less effect on the basal metabolic rate and to be less injurious to patients with less severe diabetes who are able to store it in part and who can utilize the glucose derived from its metabolism. This at least is a conclusion suggested by the results of unreported metabolism studies conducted recently by Boothby and myself. Allen and Sherrill conclude, from their experience, that "a specifically powerful glycosuric influence of protein on the ground either of its specific dynamic or supposed toxic action are proved contrary to fact." This statement seems to me to be rather strong. It is true that they were able, in several cases, to feed very large amounts of protein provided the diets were low in fat calories with a beneficial effect on glycosuria rather than the contrary. Nevertheless, when high protein was combined with many fat calories, intense glycosuria was frequently provoked. Allen and Sherrill attribute this to the fat or total calories, but the experiences of others suggest that the share of the protein should not be neglected.

Acute diseases complicating diabetes often aggravate its severity and increase the insulin requirement. Among such complications are pregnancy, hyperthyroidism and infections.

Severe diabetic acidosis may likewise affect the value of injected insulin, although the evidence for this is not so conclusive. Diabetic coma is frequently precipitated by a complicating infection, and in such cases the infection rather than the acidosis may be responsible for the disproportionate insulin requirement. Uncomplicated cases of diabetic coma have not required insulin in amounts out of proportion to the sugar available for oxidation. In a number of such cases in the Mayo Clinic we have succeeded in controlling ketosis in every instance by doses of insulin not exceeding 100 units, which is about the requirement that might be predicted on the assumption that the unit has a value of about 2 gm. The body of the diabetic patient in coma is saturated with unused sugar. The blood usually contains more than 0.5 per cent of sugar, and it is highly probable that the tissues often contain more than 200 gm. Furthermore, small doses of carbohydrate are usually given in the treatment of this condition, and also when insulin is given in doses of 300 and 400

units daily for coma, as reported from several clinics, a large proportion of it may be excreted by the kidneys.

A patient who had pernicious anemia and diabetes died recently in the Mayo Clinic in diabetic coma. The patient's condition had not been unusually severe until terminally, after a precipitate drop in the blood count. She was at her home, and intensive treatment was not instituted until she had been unconscious for two hours. During the following ten hours 200 units of insulin were totally without effect on the blood sugar or acidosis. The combination of the two diseases is uncommon. I have seen it only twice, and Adams, who is reporting these two cases, informs me that he can find only one other instance in the literature.

Hyperthyroid conditions seriously aggravate the severity of pre-existing diabetes, and the insulin requirement of patients with abnormal basal metabolic rates rises and falls with the rise and fall of the basal metabolic rate. Whether the deleterious effect of hyperthyroidism is due entirely to the increased basal metabolic rate and the consequent necessity for more food, or is in part due to an antagonism between the thyroid secretion and insulin, is at present unknown. In one of our return cases (Case A105376) severe acidosis and threatening coma were twice precipitated by a sudden exacerbation of the hyperthyroid state, and very large doses of insulin (100 units daily) were necessary. We advise thyroidectomy in cases of exophthalmic goiter and of adenoma with hyperthyroidism, not only from the standpoint of the thyroid but because thyroidectomy, by reducing the basal metabolic rate, will lessen the food requirement and thus diminish the difficulty in managing the diabetes. Also, we advise thyroidectomy for diabetic patients with adenoma of the thyroid without hyperthyroidism, not on the supposition that removal of the goiter will benefit the diabetes, but merely as a prophylactic measure designed to protect the patient from the danger of hyperthyroidism later.

The most common complication in diabetes, and one that usually increases the insulin requirement, is infection. Numerous examples might be cited. As a rule, the more severe the infection, the more seriously is sugar utilization depressed, and the larger the dose of insulin necessary to prevent acidosis. In

several instances, with diets yielding not more than 40 gm. of glucose, 100 units of insulin were given daily. In the case of a child (Case A416633), 60 units a day were necessary, although before the onset of pneumonia the case was in a mild stage of diabetes and sugar-free without insulin. Sugar continued to be excreted, and it is probable that in this instance the glucose equivalent of the insulin injected was less than 0.5 gram for each unit. Epstein reported recently that the addition of trypsin to insulin neutralizes insulin almost instantly, in a medium too acid for the neutralization to be accounted for by proteolysis. It is possible that toxins and other infectious agents exert a similar neutralizing action on insulin, and that in this manner such complications reduce the diabetic's tolerance.

In early cases of diabetes great caution must be exercised in judging the effect of treatment because marked spontaneous improvement in tolerance may be encountered. Such a case may prove to be mild after a few days of dietary regulation despite an initial appearance of severity, and if insulin has been used the erroneous conclusion may be reached that a very few units have been responsible for a greatly improved carbohydrate metabolism. The ease with which early cases of diabetes respond to dietary adjustments is responsible for the deplorable success of quackery in this field. If a drug has been used it is improperly credited with the therapeutic success. Such cases, therefore, are not suitable for the trial of new diabetic preparations, and are equally unsatisfactory as test cases for gauging the glucose equivalent of insulin.

A similar situation is presented by the many patients with benign forms of diabetes, particularly those with arteriosclerosis or obesity. As Woodyatt has pointed out, they often reveal an extreme inconsistency between the richness of the diet in carbohydrate and the degree of glycosuria. With a diet of a glucose value of 100 gm. or less, 5 to 10 gm. of sugar may be excreted, and increasing the carbohydrate of the diet by 100 gm. or more will not significantly affect the intensity of the glycosuria. Such cases are obviously unsuitable for assaying the value of insulin. There remain, however, cases of moderate and severe diabetes in which the disease has existed for a year or longer and the patients are free from acute complications. In such cases, with

diets such as we have employed, insulin apparently behaves in a very precise manner, suggesting that a quantitative relationship exists between it and glucose. Age and the size of the body affect this relationship very little, if any; the unit of insulin behaves similarly in the child and the adult. The fact that uniform general metabolic conditions are necessary for uniform results should not, it seems to me, argue against the significance of such results. Chemical reactions usually require certain constant conditions. The purity of reagents is always a matter of concern to the chemist, and for quantitative yields reagents must be mixed in suitable proportions.

#### CONCLUSIONS

1. With uncomplicated cases of diabetes of sufficient duration the glucose equivalent of the Eli Lilly Company clinical insulin unit prior to October 1, 1923, averaged about 1.7 gm., when the diet was carefully adjusted to the calorie needs of the patient and carbohydrate and protein were limited. The material now in use has not been so carefully assayed, but from general clinical observation appears to have a glucose equivalent of about 2 gm.

2. The glucose equivalent of insulin may be altered by high protein and high carbohydrate diets, and the insulin requirement of the individual may be diminished by starvation.

3. The glucose equivalent of insulin is depressed by acute complications, especially infections.

4. The fact that consistent values for the glucose equivalent of insulin have been obtained under standard conditions with patients of different ages and weights, is evidence for the assumption that the action of insulin is directly on glucose and that a definite chemical interaction occurs between insulin and glucose.

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# BRAIN DEVELOPMENT IN ANURAN LARVAE AFTER THYROID OR PITUITARY GLAND REMOVAL

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LOS ANGELES

This work is a part of a series of studies on the influence of the endocrine glands upon the development of larval amphibians. A general account of the brain of thyroidless *R. pipiens* larvae was given Allen '17. It was shown that this organ seen in surface view retains its immature condition in a stage corresponding with the degree of development of the hind legs and general body form. Even in tadpoles that had lived many months beyond the usual time of metamorphosis and had attained a size much greater than normal, the brain was found to correspond closely with the general bodily development. This early paper did not go deeply into the subject because a detailed study was left for a later time. The importance of this line of work is readily inferred from the fact that cretinism in man is so notably attended by mental deficiency.

E. R. and M. M. Hoskins '19 published views at variance with these, claiming that while there is a temporary retardation of the development of the brain to correspond with that of the body as a whole, nevertheless the later development of the brain brings it finally to about the condition to be found in the metamorphosed frog.

The writer has repeated his observations upon the surface appearance of a large number of brains of these thyroidless tadpoles ranging from a few months to as much as three years of age, but has failed even in the oldest to find any marked progress in brain development beyond that which corresponds to the general bodily development. There are certain special features that are distinctive, but they are not in the direction of development in metamorphosis. These will be discussed below.

The writer's study of transverse sections has proven to be especially instructive, showing clearly the undeveloped character of the brain in these larvae that are in so many other fea-

tures held in their immature condition. Similar observations, giving like results, were made upon the brain of *Bufo americanus* and were published in a preliminary account but are now furnished in full for the first time.

An article by Werner Schulze '24 fully substantiates these conclusions, "Gehirn und Rückenmark, des thyreoprivten Tieres (tadpole) zeigen Organsysteme wie sie ihrem Bau und ihrer relativen Grösse nach für Larven charakteristisch sind. Aus dem Umstand, dass die Organe bis zu dem Tode des Tieres normal funktionieren, kann man ausserdem den Rückschluss machen, dass sie in ihrem Funktionszustand dem Larventyp des Tieres adäquat waren."

The material upon which this work is based was collected at Lawrence, Kansas. The fixing fluid used was bichromate-acetic. The thyroid and pituitary glands were removed at their inception by the methods explained in earlier papers (Allen '16, Allen '17). The tadpoles were reared under conditions of food and surroundings identical with those of the controls. The brains were dissected out, drawn with camera lucida, stained in toto in alum cochineal, and cut in serial section. The drawings of the whole brain were all made to a common scale and the sections were likewise treated uniformly on a somewhat larger scale. The transverse sections shown in the drawings and taken as a basis for comparison of the internal features of the brain were carefully selected to show corresponding regions of the brain, as follows:

1st. Immediately in front of the caudal point of union of the cerebral hemispheres;

2nd. Through the diencephalon at a point two-thirds its length behind its cranial end;

3rd. Through the center of the mesencephalon (optic lobes);

4th. Through the myelencephalon immediately behind the cerebellum.

The drawings were all made with the aid of camera lucida, with an aim to strict accuracy in the representation of relative size and general features of outline. The areas of nuclei are shown as well as possible, but such cellular details are only in few cases considered as a basis for the conclusions drawn. There

was little difference in the treatment of *Rana* and *Bufo*, save for the fact that in *Bufo* lateral views of the brains were included and a study was made of the brains of tadpoles deprived of the pituitary gland. See pages 644 to 651.

It is not necessary to enter into a lengthy description of the figures because they tell the story in themselves. We can gain our orientation from examination of the drawings of the whole brains of both *Rana* and *Bufo*. In the first place, there is a far greater difference in the degree of development of the brain of the thyroidless tadpoles as compared with that of the normal controls in the case of *Bufo* than in *Rana*. This is equally true when we compare the size of the body as a whole. This may be correlated with the clearly observed fact that the hind legs grow relatively longer in thyroidless and pituitaryless larvae of *Bufo* than in those of *Rana*. This has been interpreted as due to a greater tendency in *Bufo* to develop independently of these glands. The basic factors that control development, other than the endocrine glands, can carry *Bufo* further than *Rana*. It will be seen that this is not only true of limb growth, but that it is manifested in the development of the general form of the brain. The specimen of thyroidless *Bufo* selected for illustration and study was the largest and most highly developed of all, yet it still shows brain characteristics that are for the most part larval. This was a case of extreme development. A number of other brains of *Bufo* thyroidless tadpoles showed far more decided larval characteristics than this.

In the *Rana pipiens* and *Bufo americanus* the control larvae chosen for comparison were taken at a stage when the hind legs bear the same relation to body length that they usually have in thyroidless and pituitaryless tadpoles some months after the period when metamorphosis normally occurs. This is the stage with which we should properly compare the experimental specimens even despite the frequent differences in size. In *Rana* the differences between the brain of the control tadpoles of this stage as compared with that of the stage immediately after metamorphosis is very clearly seen. The young tadpole has rather weakly developed cerebral hemispheres, the diencephalon is narrow and elongated, the optic lobes are nearly hemispherical, and the fourth ventricle is elongated.

After metamorphosis the cerebral hemispheres are found to have elongated, the diencephalon has broadened, the optic lobes have become oval, meeting one another with their long axes at right angles. The fourth ventricle has become much shortened and the sides are rolled inward.

In the thyroidless tadpole the cerebral hemispheres, typically shorter than those of the normal tadpole, are dilated by the enlargement of the ventricles. The diencephalon is relatively narrower than in the metamorphosed specimens and more closely resembles that of the larval controls. The optic lobes are clearly like those of the normal larvae, and the fourth ventricle shows the same form. Certain special features are seen in the distended character of the cerebral hemispheres and the widening of the myelencephalon.

The pituitaryless tadpoles have brain features in every way comparable to those of the thyroidless specimens. There is little difference between them aside from the features that result from differences in size.

In transverse sections it is seen that metamorphosis causes a narrowing of the first and second ventricles. This is partly but not wholly due to the thickening of the median walls of the cerebral hemispheres. After metamorphosis there is a marked density of neuroblasts in this median thickened wall. The third ventricle is narrowed, its walls much broadened, and the nuclei embedded in them show a marked increase in number. Similar features appear in the optic lobes, while the myelencephalon becomes decidedly narrower and thicker.

In thyroidless and pituitaryless tadpoles the broadening of the cerebral hemispheres and the dilation of their ventricles is very marked. This is a constant character in all of the specimens studied. The diencephalon is in the main rather irregular in outline and the third ventricle is broader than in the metamorphosed specimens. In the brain of the giant thyroidless *Bufo* tadpole shown, this feature is less evident than in any of other specimens studied. Transverse sections of the optic lobes in the thyroidless and pituitaryless tadpoles show the same wide aqueduct of Sylvius seen in the larval controls. Finally, in the sections of the myelencephalon is seen one of the most constant and striking peculiarities, this structure being spread out

broadly with a wide open fourth ventricle. The walls are relatively far thinner than we find them to be in the metamorphosed specimens. While the resemblance of the myelencephalon of the specimens operated upon and the larval controls is unmistakable, the former yet have certain features that are peculiar to them, notably the hydrocephalous character of the cerebral hemispheres and the great breadth of the myelencephalon.

Cooksie '22 has shown that thyroid feeding causes the brain to develop toward the form found at metamorphosis. This is accompanied by decided deformity due to strong shrinkage of the brain case with little reduction in the size of the brain-itself.

We might thus conclude that the brains of tadpoles from which the thyroid or pituitary glands have been removed tend to retain characteristics found in larvae of corresponding stages of bodily development. There are certain special features that mark them as pathological, but these are less significant than are the points of similarity to the larval conditions. The brain then follows the general rule so well illustrated in the other somatic organs that the tadpole retains its larval character both externally and internally when the thyroid gland or the pituitary gland is removed. While there are certain special features in these experimental tadpoles, the general conclusion given above is unmistakable.

Grateful acknowledgment is made for research grants by the University of Kansas and later by the University of California for the support of this work.

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## PLATE I.—SURFACE VIEWS OF BRAINS OF RANA

## PIPIENS. X-10.

Figs. 1 and 2. Normal control after metamorphosis. Total length 20.9 mm. Hind leg length 26.1 mm. Fig. 1, Dorsal. Fig. 2, Ventral.

Figs. 3 and 4. Thyroidless tadpole. Total length 88.7 mm. Trunk length 42.1 mm. Hind leg length 4.49 mm. One and one-half years old. Fig. 3, Dorsal. Fig. 4, Ventral.

Figs. 5 and 6. Larval control. Total length 63.7 mm. Trunk length 26.3 mm. Hind leg length 4.4 mm. Fig. 5, Dorsal. Fig. 6, Ventral.

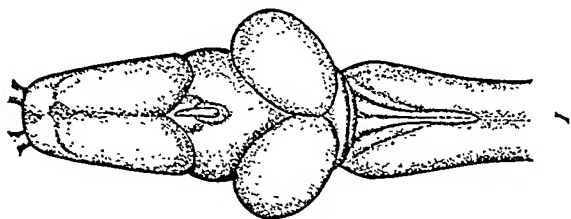
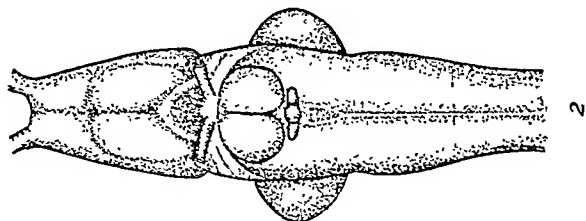
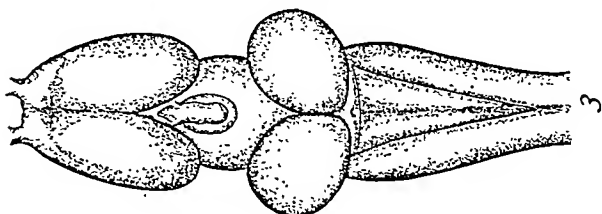
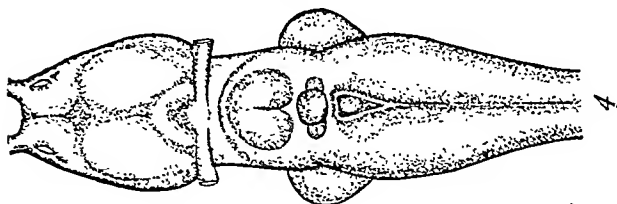
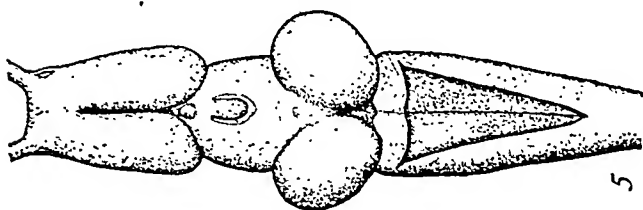
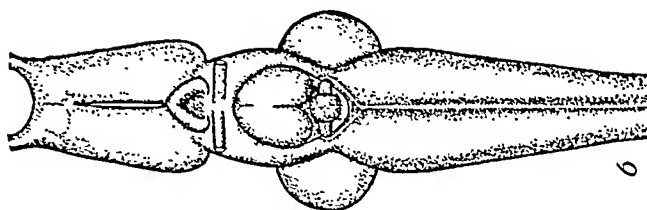




PLATE II.—TRANSVERSE SECTIONS OF BRAINS OF RANA  
PIPIENS. X-15.

Figs. 7 to 10. Normal metamorphosed controls (shown Pl. I., Figs. 1 and 2). Fig. 7, Cerebral hemispheres. Fig. 8, Diencephalon. Fig. 9, Optic lobes. Fig. 10, Myelencephalon.

Figs. 11 to 14. Thyroidless tadpoles (shown Pl. I., Figs. 3 and 4.) Fig. 11, Cerebral hemispheres. Fig. 12, Diencephalon. Fig. 13, Optic lobes. Fig. 14, Myelencephalon.

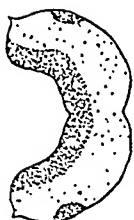
Figs. 15 to 18. Pituitaryless tadpole (shown Pl. I., Figs. 5 and 6). Fig. 15, Cerebral hemispheres. Fig. 16, Diencephalon. Fig. 16, Optic lobes. Fig. 18, Myelencephalon.



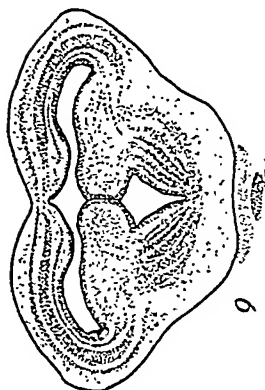
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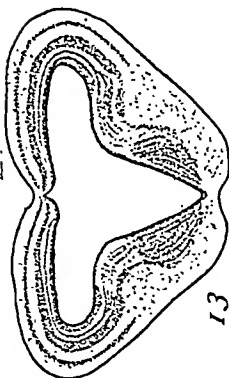
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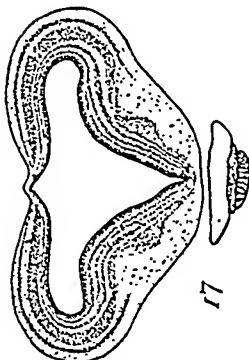
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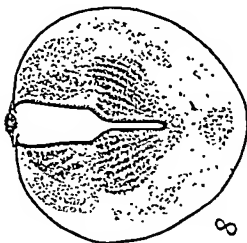
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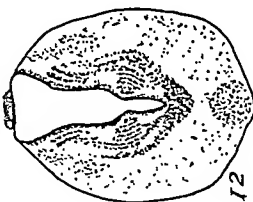
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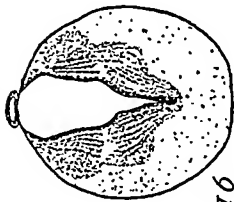
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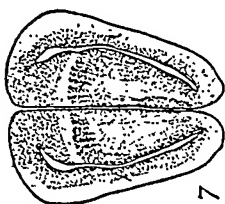
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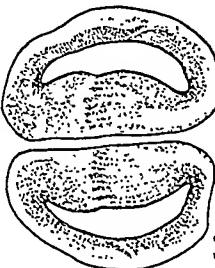
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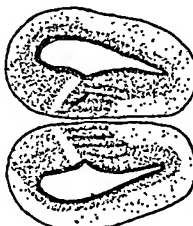
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PLATE III.—SURFACE VIEWS OF THE BRAINS OF BUFO  
AMERICANUS. X-10.

Figs. 19 to 21. Normal controls after metamorphosis. Trunk length 11.2 mm. Hind leg length 10.7 mm. Fig. 19, Dorsal view. Fig. 20, Ventral view. Fig. 21, Lateral view.

Figs. 22 to 24. Normal control tadpole. Total length 20.7 mm. Trunk length 10.7 mm. Hind leg length 7.3 mm. Fig. 22, Dorsal view. Fig. 23, Ventral view. Fig. 24, Lateral view.

Figs. 25 to 27. Pituitaryless tadpole. Total length 27.6 mm. Trunk length 14.6 mm. Hind leg length 3.6 mm. Killed May 17. Fig. 25, Dorsal view. Fig. 26, Ventral view. Fig. 27, Lateral view.

Figs. 28 to 30. Thyroidless tadpole. Total length 40.0 mm. Trunk length 19.7 mm. Hind leg length 4.88 mm.

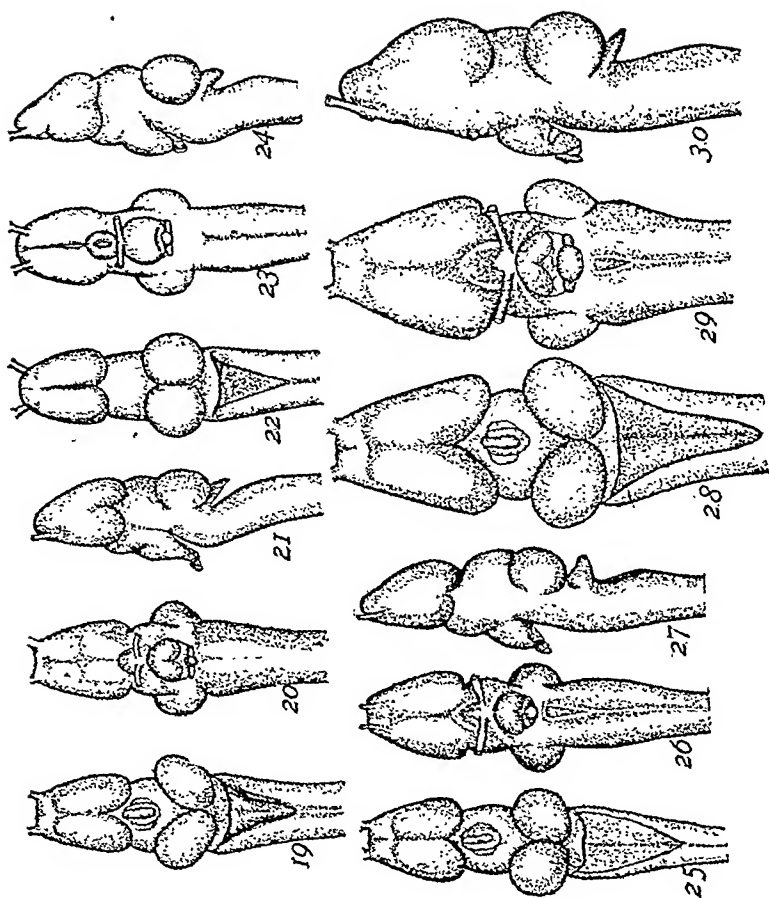
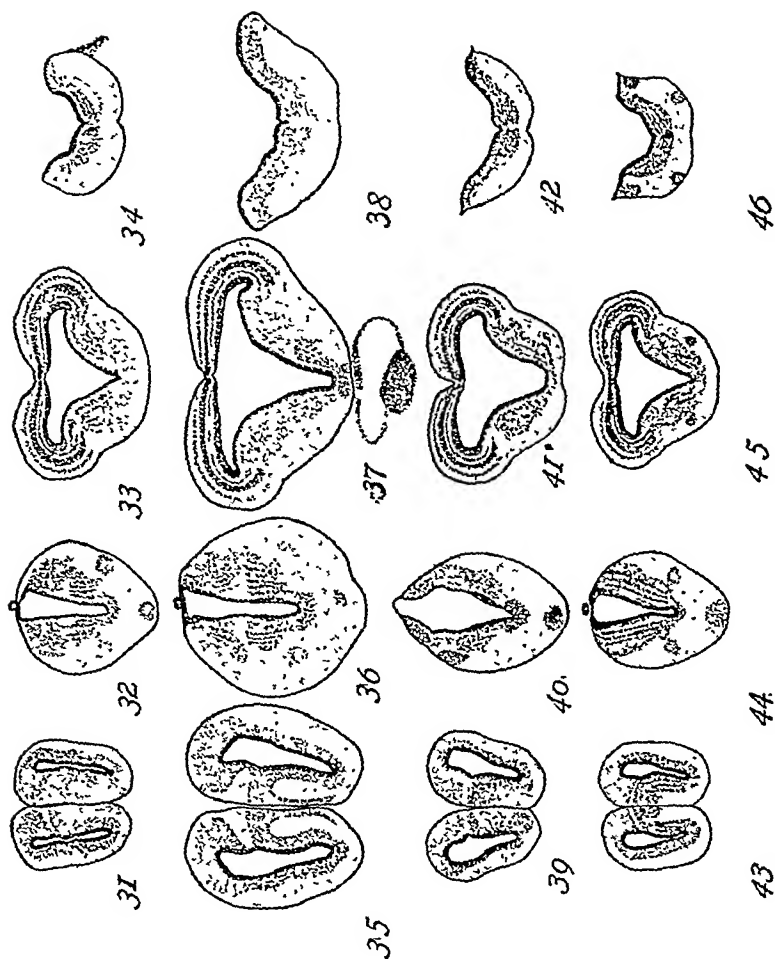


PLATE IV.—TRANSVERSE SECTIONS OF BRAINS OF BUFO  
AMERICANUS. X-15.

Figs. 31 to 34. Normal metamorphosed controls (shown Pl. III., Figs. 19-21). Fig. 31, Cerebral hemispheres. Fig. 32, Diencephalon. Fig. 33, Optic lobes. Fig. 34, Myelencephalon.

Figs. 39 to 42. Pituitaryless tadpole (shown Pl. III., Figs. 25-27). Fig. 39, Cerebral hemispheres. Fig. 40, Diencephalon. Fig. 41, Optic lobes. Fig. 42, Myelencephalon.

Figs. 43 to 46. Normal control tadpoles (shown Pl. III., Figs. 22-24). Fig. 43, Cerebral hemispheres. Fig. 44, Diencephalon. Fig. 45, Optic lobes. Fig. 46, Myelencephalon.



# HYPEROVARIANISM AND ITS SPECIFIC TREATMENT

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## OVARIES AND MENSTRUATION

Although there have been many noteworthy accomplishments in endocrinology, especially during the past two years, yet we know very little with regard to the functions of the various elements of the ovaries. Even concerning the causation of menstruation, which of course is the most striking of the phenomena by which the ovarian activity manifests itself, endocrinologists and gynecologists disagree, some following the opinion of Fraenkel, according to whom the menstrual cycle depends upon the corpus luteum; and others holding the opinion of Schickelé, recently accepted by Henry and Ramírez, according to whom the corpus luteum rather has an inhibitory action upon menstruation.

In an article published in this journal not long ago, Novak (1) of Baltimore said: "Again the studies of Fraenkel, followed later by those of Meyer, Schroeder, Ruge, and others, appear to have demonstrated conclusively that the corpus luteum is the element in the ovary which is responsible for the occurrence of the menstrual cycles, and the chronological relationships of the ovarian, endometrial and menstrual cycles have been quite satisfactorily worked out."

Blumgarten (2), of New York, still more recently states: "The importance of the corpus luteum in menstruation has been established."

On the contrary, Henry (3), of Paris, having studied the condition of the corpus luteum in different stages, found that: "Il y a des femmes régulièrement menstruées chez lesquelles on ne décèle aucun corps jaune en évolution." Holding the same view, Ramírez (4), of Mexico, stated that: "Not only does the corpus luteum have no function in initiating menstruation, but its presence impedes the menstrual onset."

## HYPEROVARIANISM

Our knowledge of ovarian syndromes is likewise defective. It is true that we know well the symptoms (anovarianism) which follow ovarian extirpation, but we know only a little about the real ovarian insufficiency (hypovarianism) and still less concerning ovarian hyperactivity (hyperovarianism). I wish to point out that the existence of hypergenital syndromes has been denied even by Pende (5), who in 1915 emphatically asserted that "*Sindrome cliniche di esagerato sviluppo sessuale e di esagerata funzione sessuale, dovute ad un processo morboso delle glandole genitali, noi non ne conosciamo.*"

However, if we review the recent literature on this subject, we shall find a few symptoms which may be referred to the hyperovarian syndrome. They are the following:

1. Precocious or excessive menstruation.
2. Uterine and mammary congestion.
3. Intermenstrual leucorrhoea.
4. Metrorrhagias.

Moreover, some cases of precocious puberty, genital hypersensitiveness, and exaggerated emotivity during the menstrual period, seem to be due to any disturbance of the ovary. However, the hypophysis and the thyroid may also have a part in the causation of these phenomena.

## TREATMENT OF HYPEROVARIANISM

As far as therapeutics is concerned, we have no specific means for the treatment of ovarian hyperactivity. All the means which have so far been used for this purpose must be considered either palliative or even harmful. They may be arranged as follows:

- (a) Chemical means: hemostatic substances.
- (b) Physical means: cold applications; x-ray therapy.
- (c) Mechanical means: ligation of the vessels; partial excision; total extirpation.

The use of hemostatic substances is empiric and usually proves to be harmful to the patient.

Cold applications as a symptomatic therapy are merely palliative. X-ray therapy must be used carefully and is to be



changes, may excite these glands when they are in a condition of deficient activity, as seems to be the case in hyperovarianism, thereby establishing the hormonal equilibrium.

By giving this paper for publication I wish not only to call the attention of all those who are interested in the further development of the methods of treatment of endocrine diseases to the action of the serum of ovariectomized animals, but also to ask their co-operation in the solution of this new endocrinological problem.

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# PARATHYROID TETANY \*

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The parathyroid glands have long been regarded as internal secreting organs, whose product plays an extremely important part in metabolism and whose absence quickly leads to the death of the individual in profound depression or more commonly in a state of great nervous excitation, the so-called parathyroid tetany. The recent development by the author and his associates (1) and by Luckhardt and his co-workers (2) of several methods by means of which this post-operative depression and tetany may be entirely prevented and controlled has brought out the important fact that dogs may be kept alive for years and perhaps a normal life span with no trace of parathyroid tissue, as at present defined, in the body. This statement is made with a full realization of the demonstration of supernumerary and accessory parathyroid glands in a varying per cent of animals in different species, and I believe it to be a fact. Every investigator who has worked long in this field has met with animals which showed neither tetany nor depression after what was supposed to be a complete parathyroid extirpation and which survived indefinitely thereafter in good condition and free from tetany. Such occasions are not many in the dog but vary greatly in other species. In many of these survivors accessory parathyroid tissue has been found in the neck, in the thymus, or along the trachea, aorta or pulmonary artery. When, however, the thyroid and parathyroid glands in the dog are widely extirpated and no glandular tissue is left in the neck, not more than five or ten per cent of these animals will survive more than two weeks without treatment. In my experience of over one hundred thyro-parathyroidectomies in the dog, only three per cent survived. Simpson (3) reports no survivals, in over one hundred complete operations. The literature on this point is not very val-

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\*Read at the Eighth Annual Session of the Association for the Study of Internal Secretions, Chicago, June 9, 1924

uable since not many authors have operated upon enough dogs to make their statistics significant. Those in which authors claim to have removed all the parathyroids leaving the thyroids intact should not be considered, because of the great probability of some parathyroid cells remaining imbedded in the mass of the thyroid glands which were left. When, then, it is possible by the method of treatment to be described below to preserve from 75 to 90 per cent and perhaps more of dogs from which both thyroids and parathyroids in the neck have been removed, the significance of these methods cannot be doubted.

One may, however, still argue—and some (4) apparently prefer to do this—that all dogs have accessory parathyroid tissue some place in the body. This assertion cannot be disproved, but it would be still more difficult to prove it. One might conceivably make serial sections of the entire animal and examine these painstakingly under the microscope for cells that histologically resemble those of the parathyroid gland. But if they were found it would still devolve upon the investigator to prove that they were functionally identical with the glands in the neck.

In a report before this association in St. Louis two years ago I described a method by means of which male and non-pregnant female dogs could be kept alive and free from tetany following complete thyro-parathyroidectomy. The principle of the method involved the prevention of bacterial proteolysis in the intestines by special diets. These early experiments have been confirmed and amplified, and we may now definitely say that over 90 per cent of completely thyro-parathyroidectomized dogs may be kept alive by this method. At about the same time, Luckhardt found that similar results could be obtained by an entirely different method, namely, the intravenous injection of large amounts of Ringer's solution. Some time later Luckhardt and Goldberg found that the oral administration of calcium lactate in large amounts was quite as effective in the control and treatment of parathyroid tetany as the two previous methods.

While the interpretation of these findings is perhaps unsettled, their accuracy and great significance cannot be questioned. At the present writing we have treated eighty dogs in which a complete thyro-parathyroidectomy had been done, by either one or a combination of the methods described above.

Seventy per cent of these have survived for two months to two years. Included among the 30 per cent that died within the two-month period are those killed by accident or which died from intercurrent infections. Such a large percentage of recovery cannot be explained on the basis of the presence of accessory parathyroid tissue, as at present anatomically and physiologically defined.

If a ten-kilogram male or non-pregnant female dog be placed on a diet consisting of 75 grams of lactose, 500 cc. of milk, and white bread ad libitum per day, tetany or depression will not develop following thyroid and parathyroid removal. It was found advisable to continue this diet for two weeks before operation, when the feces became liquid, colorless, acid to litmus, and the fecal bacteria predominantly aciduric in type. After-operation the animal was fed daily with the stomach tube for at least a month. Such a dietary regimen checks bacterial proteolysis or putrefaction in the intestinal tract and accordingly prevents the formation of the highly toxic protein derivatives commonly resulting from such action.

It has been demonstrated by the author (5) that the toxicity of the intestinal content depends in largest part upon these toxic protein derivatives arising from bacterial proteolysis, and the interpretation placed upon these experiments depends upon this fact. Parathyroid tetany is an intoxication and the responsible toxic substances come chiefly from the gastro-intestinal tract. The discovery by Luckhardt and Rosenbloom that parathyroid tetany or depression can be entirely prevented or controlled by the daily administration of large amounts of Ringer's solution intravenously is in harmony with this view. The vigorous diuresis induced by such injections might well remove from the blood the toxic materials responsible for the tetany. This explanation has, however, lately been modified by Luckhardt and Blumenstock (6) through the realization of the role played by calcium in Ringer's solution. Other solutions, free from calcium but producing greater diuresis than Ringer's solution were not quite so effective in controlling the tetany. The relief that may be obtained by the intravenous injection of calcium lactate in a dog in violent parathyroid tetany, as demonstrated by McCallum and Voegtlin and others, is indeed, as Berkeley and

Beebe remark, "one of the most striking in the range of physiological experimentation."

The fact, however, that parathyroidectomized dogs may be kept alive and free from tetany for indefinite periods by the daily oral administration of 20 to 30 grams of calcium lactate is perhaps of still greater significance. The role played by the calcium is not readily understood. At the present time it cannot be said with certainty whether the calcium supplies a specific physiological deficit in the organism or merely controls the syndrome of parathyroid tetany by its pharmacologic action. The latter possibility becomes more evident when it is realized that if the parathyroidectomized dog is carried safely through the first six or eight weeks by any one of the three methods, he may thereafter survive in good condition without further treatment.

The prevention of parathyroid tetany by checking bacterial putrefaction in the gastro-intestinal tract indicates certainly that this must be the chief source of the tetany poisons in male and non-pregnant female dogs. Tetany in pregnant dogs cannot, however, be controlled by this method. It can, however, by the intravenous injection of Ringer's solution, and it appears very probable, accordingly, that during pregnancy poisons, capable of causing tetany, may arise elsewhere. The available evidence indicates that the pregnant uterus may supply such toxic materials, and in this sense tetany may be considered as one of the possible toxemias of pregnancy. Parathyroid tetany in pregnant dogs may also be prevented and controlled by the oral administration of calcium lactate. Larger amounts are necessary than suffice for non-pregnant animals. Thus, if this calcium salt exerts an antitoxic action, its influence is not only local but must extend also to poisons in the blood stream.

Oestrus and lactation are likewise special conditions during which tetany may appear on parathyroidectomy, even if all bacterial putrefaction in the gastro-intestinal tract has been prevented. This tetany may, however, be controlled by the intravenous injection of Ringer's solution or the oral administration of calcium lactate. It is possible that the changes in the uterine mucosa during oestrus may occasion the local production of toxic substances which enter the blood stream and cause tetany. The withdrawal of calcium in the milk, however, is certainly a factor

which must be considered in the pathogenesis of the tetany of lactation.

A complete analysis of the pathogenesis of tetany must take cognizance of the facts indicating the presence of an intoxication and also of the facts developed with regard to the role of calcium and perhaps other inorganic salts in this condition. There are no facts irreconcilable with the view that tetany is a toxemia, and there is much evidence to support it. The control of tetany by certain calcium salts does not disprove this view and when more is learned concerning the action of calcium it is probable that the apparent contradictions will vanish. It is not probable that the toxemia is due to any one chemical substance, or indeed to the same substance in all species of animals. The chief source of these toxins in the dog and probably also in all carnivorous animals is bacterial putrefaction in the intestinal tract. They may, however, also come from the uterus in pregnancy or from bacterial products in case of infections. We have not yet secured definite evidence of their endogenous origin, that is, as a product of normal cellular metabolism.

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#### (DISCUSSION ON PAPER OF DR. DRAGSTEDT)

Dr. Arno B. Luckhardt, Chicago: The methods employed by us in the investigation of the prevention and possible cause of tetany are quite different from those fundamental considerations which prompted the experimental work of Dr. Dragstedt. It is an interesting thing that in spite of the fact that the basis of the experimental work is entirely different, the interpretation of the results is almost identical. I am in thorough agreement with Dr. Dragstedt that the cause of tetany is intoxication, that it is not a diminution of calcium *per se* or what might be called a hypocalcemia.

As outlined by him, our methods were the intravenous injection of a solution of calcium which we are told would be ineffective. Just

how the administration of calcium keeps the animal normal after parathyroidectomy is not quite clear. We started with the administration of calcium lactate, but recently, in the past six months, decided to test out the efficacy of other calcium compounds, and Mr. Tumpeer and myself tested out calcium acetate and calcium phosphate. These are quite as efficient as calcium lactate except calcium phosphate. Calcium phosphate, when given in quantities by mouth, rather predisposes to the onset of tetany rather than cures it. There may be some relation between the injection of calcium phosphate and the more rapid absorption. Tentatively, I have assumed that the hypocalcemia described in tetany is rather the effect of the tetany than its cause. The calcium compounds might be acting in the gut by changing the metabolism of these protein products as Dr. Dragstedt said. Calcium might act in the gut by neutralizing the hypothetical toxins which are supposed to be responsible for the tetany. Calcium is known to change the permeability of the gut. If that were the explanation these hypothetical compounds might not be able to pass through the gut and could accumulate in the tissues and in the blood stream and thus predispose to tetany. That the permeability of the gut is a factor in the genesis of tetany is evidenced by the findings of Tumpeer and myself as indicated by the fact that any maneuver to change the permeability of the gut will promptly throw the animal into tetany. We worked on animals that had survived complete thyroidectomy for 40 to 60 days. We put them on a specific meat diet which was supposed to produce tetany and they did not develop it. By giving a brisk cathartic to produce an enteritis and change the permeability of the gut we were able to throw these animals into tetany later. That tetany was promptly controlled by the thorough administration of calcium compounds, except phosphate. That observation would support the view that the calcium compounds act in the gut by making it less permeable. We can assume that a change in the permeability following the removal of the parathyroids leads to a greater excretion of the gut, that the removal of the parathyroids permits circulation into the gut with greater ease. It is known that the chief route of excretion of calcium is through the gut. The greater excretion of calcium into the gut will account for the hypocalcemia which is described. I repeat again from the present point of view that hypocalcemia which has been described can be considered the effect of tetany rather than its cause. I am in thorough accord with Dr. Dragstedt's views.

Just one word as to the result of the injection of calcium compounds. Those who have used this method recognize the fact that animals fail to survive following intravenous injection of calcium compounds in spite of the fact that the early results were beneficial. The literature is full of protocols of animals that died in spite of the intravenous injection of calcium. We have an accurate explanation for these failures, that when calcium salts are injected they have a nephrolytic action. In one animal the intravenous injection of calcium salts produced an anuria and there was 17 per cent albumen. It has been shown that the injection of these compounds exerts a deleterious effect on the kidney parenchyma due to the fact that these toxins are so soluble. I can well understand why those who tried to keep such animals alive did not succeed. They overlooked the chief factor, the excretion of the kidney. As a result of that the animals died from tetany, not in spite of the intravenous injection of calcium, but because of it.

Dr. Walter M. Boothby, Rochester, Minn.: We have had at the Mayo Clinic in the past two years three cases of parathyroid tetany, and, of course, it has been incumbent upon us to keep them alive. This work of Dr. Dragstedt and Dr. Luckhardt is exceedingly impor-

tant. I will not enter into detail as to whether the cause is due to lack of calcium or whether it is due to toxemia. From the clinical point of view at the present time that is the least interesting, though of course it is a vital problem to work upon.

We have approximately 1500 thyroidectomies a year and we usually have out of that number one or two cases of parathyroid tetany; that is, it occurs in about 1 in 1500 or 1 in 1000 cases of thyroid operation that we perform. It is an accident that must be taken care of. This work that Dr. Dragstedt has reported, and also Dr. Luckhardt's, has helped us a great deal in keeping these patients alive. We have confined our attention mainly to keeping up the blood calcium. Clinically about four days or three days after operation the patient who is going to have parathyroid tetany will feel a twinge of the facial nerve. If that occurs twice we can be sure that the blood calcium is becoming decreased. Ordinarily the blood calcium will run about 10 mg. About the third day when the patient shows the first sign of tetany the blood calcium will be down to the region of 7. It is then necessary to start the calcium and keep the blood calcium up above 7, which seems to be the critical line, to prevent tetany.

The administration of calcium is a trick that has to be learned. In the first place, calcium lactate has to be dissolved in water. In the second place, it must be given in large doses and not too frequently. Sixty grains dissolved in water every three hours day and night are required at first, but as time proceeds there seems to be a readjustment. We have assumed that this is a readjustment of a non-organic substance. At all events, the individual will be able to run along very well with the blood calcium low, better than he did at first. For instance, after two or three months he will not go into tetany when the blood calcium drops down to 6 or 7. He seems to be able to stand that concentration much better than at first. He will, however, go into tetany again if the calcium is stopped, and also show a marked drop in the blood calcium line.

Intravenous calcium is not good: one cannot inject very much, and sloughing due to accidental introduction of the salt into the tissues about the puncture is likely to occur.

Surgeons, when they see a case of parathyroid tetany are likely to get alarmed and want to give an intravenous injection. This is a surgical procedure. Parathyroid tetany in the human being can be controlled in one-half hour by giving calcium lactate by mouth, if it is given in large doses. We let the patient develop actual tetany before we start the calcium, because there are a certain number of hysterical manifestations after thyroid operations that have a similarity to those of patients with low blood calcium. These patients are perfectly well taken care of by the ordinary routine treatment. If there are any cramps, if the fingers are drawn up, with fine twitches, with the legs drawn up, if they are in severe pain, the thing to do is to give calcium lactate every 15 minutes until they are out of it, and then every two or three hours for two weeks. Then the dose can be decreased until the body has become adjusted to the lower calcium level.

Dr. W. F. Walter, Washington, D. C.: I am very much interested in the paper which Dr. Dragstedt has presented, and particularly interested in the fact that he removes the entire thyroid gland as well as the parathyroids. I should like to ask Dr. Dragstedt if in these animals that have died there has been a post-mortem examination, and what pathological conditions were found in the other endocrine glands; also, in the female dogs which have been operated on, if pregnancy has occurred in any of them. Perhaps I had better state it rather under my breath, but in patients suffering from exophthalmic goiter I was taught to leave two-fifths of the gland, and I did it



with many recurrences and more incomplete recoveries. Then I left only one-fifth, and then less and less, until I have removed from seven patients suffering from exophthalmic goiter the entire thyroid gland. These patients are still alive and they are not suffering from any hypothyroid symptoms or myxedema. I would like also to ask Dr. Dragstedt if these dogs showed any signs of myxedema.

Dr. J. P. O'Neil, Chicago: Two years ago I first heard of the work of Dr. Dragstedt and Dr. Luckhardt, and about the same time I had a case that came into this field. It was a woman who had a history of epilepsy at the age of 28. She had never been operated on for thyroid disease, though she had a large adenoma removed four or five years later. The first attack of epilepsy occurred at 17, the second at 28. They always came on following excitement. At about the age of 30 she began to have more attacks, and at about 35 they began to come on once a week or once every two weeks. The peculiar thing about the case was this: if the attack began on Friday she would run continuously on Friday and therefore the probability of hysteria had to be considered. She had consulted some of the best neurologists in Chicago, in the East and in the South, and the unanimous opinion was that it was a true epilepsy.

Following the idea of Dragstedt and Luckhardt—and a little before that—I had begun working on the basis that it was an endocrine disturbance. No previous treatment had been of any avail. It had not been possible at any time to get the feces absolutely odorless or colorless. Since beginning treatment she has had three separate attacks in two years, each one of which could be attributed to the fact that she had partaken of a diet high in protein and high in meat. She would know six or eight hours before that an attack was approaching. It usually followed a sleepless night. Many of them have been averted but she has had three.

Dr. Lester R. Dragstedt, Chicago (closing the discussion): Dr. Luckhardt and I worked from an entirely different angle. I would like to emphasize again that there is no real contradiction between the work on calcium, the relief of parathyroid tetany by the administration of calcium, and the experimental and clinical observations indicating that the condition is a toxemia. Much might be said with regard to this view of the pathogenesis of tetany in analyzing the various types of clinical tetany, tetany in children, in gastro-intestinal disorders, after infection, after toxemias, after intestinal obstruction, etc.

I was very much interested in the report by Dr. Boothby of the use of calcium in clinical parathyroid tetany. We have seen a number of such cases respond to calcium administration in the same way that our experimental animals responded. There is nothing to indicate that the clinical parathyroid tetany is any different from experimental parathyroid tetany.

With regard to the adjustment or compensation which occurs in animals or man after parathyroid extirpation we may report this experiment: If the animal has been controlled by any method following complete thyroidectomy for a period of six to eight weeks, he thereafter may remain in good condition without treatment. It is possible that some adjustment has taken place in some of the other organs so that they may have taken over the function of the missing glands. The administration of phosphorus to animals that have been relieved will throw them into violent tetany, the symptoms being the same as those following acute removal.

A number of parathyroidectomized animals have come to autopsy. Some of them died spontaneously and some were killed. These animals showed no definite pathologic lesions in any of the organs. We

have thought that there might be a slight enlargement of the adrenal glands but that cannot be stated with any degree of certainty.

A number of these animals that have been operated on and recovered have become pregnant. It is interesting that these animals which became pregnant following complete parathyroidectomy and had been normal for a month or so, during the latter part of pregnancy developed violent convulsions, much like those occurring in animals recently operated on, and there were many things in this condition which suggested the convulsions occurring in pregnancy with eclampsia. I would not, however, like to give the impression that it is possible to completely cure the animal after removal of the parathyroid glands. These animals, although they may survive for a long period apparently normal, are not normal animals. They will develop tetany convulsions in case of pregnancy or oestrus, which resembles menstruation in the woman. Dr. Luckhardt noted in a number of his animals that months after operation, though the animals seemed normal, they developed bilateral cataracts. My animals showed exactly the same condition. Cataracts will begin in three months or six months and will lead to complete opacity of the lens.

It is interesting that we have not seen in any of our animals symptoms of myxedema. There can be no question but that we removed all the thyroid tissue in the neck because we were not afraid to remove it. We tried to remove all the thyroid tissue and all the parathyroid tissue and we succeeded in perhaps 50 to 60 animals and kept them alive for a period of six months to two years. These animals did not develop myxedema. In many that were examined at autopsy we have not been able to find any trace of thyroid tissue in the chest. It may be that myxedema is a defect in metabolism which is manifested only in young animals. All the animals on which we operated were adults.

# FURTHER OBSERVATIONS ON FEEDING INTERRENAL GLAND IN CASES OF GRAVES' DISEASE \*

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In 1921 Marine and Baumann demonstrated that sublethal but sufficient destruction of the function of the interrenal glands in rabbits caused a sustained rise in heat production. Scott, working with cats, confirmed their results. The animals at autopsy showed thyroid hyperplasia and hypertrophy of the lymphoid tissues, particularly the thymus. From their results, these authors maintained that there exists an interrelation between the thyroid and the interrenal glands, the latter exerting an inhibitory or regulatory control over the thyroid. A functional interrenal insufficiency would consequently cause increased thyroid activity, its iodine store would become exhausted, which in turn would cause hyperplasia of the alveolar epithelium. From these and other experimental data they suggested that a functional interrenal insufficiency plays a fundamental role in the development of Graves' disease. Upon this basis we have been feeding ox interrenal glands to subjects of Graves' disease. On empiric grounds Solis-Cohen in 1896 and Crary in 1897 used desiccated preparations of suprarenal glands in the treatment of this condition.

In November, 1921, we published a clinical report of our first case so treated. This patient, in addition to other manifestations of improvement, showed rapid gain in weight (8.6 kg. first month and 10 kg. second month) and improvement in muscle strength following the oral administration of fresh ox interrenal glands. Since then we have studied the effects of feeding interrenal gland in a series of twenty cases of Graves' disease. The age groups of these patients were as follows: one was 9 years old; four were between 16 and 20 years; ten between 31 and 38; four between 40 and 48, and one was 62 years old.

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\* Read at the Eighth Annual Session of the Association for the Study of Internal Secretions, Chicago, June 9, 1924.

All except two were females. Two of the subjects had had x-ray treatments of the thyroid area before admission but without improvement.

The preparation used by us was a 50 per cent glycerol emulsion of fresh ox interrenal glands. This is made in the following manner: the glands are carefully freed of fat and then split sagittally; the medulla is carefully dissected out with scissors (if well done this removes approximately 90 per cent of the epinephrin containing tissue); the cortical portion is then hashed and mixed with equal parts by weight of glycerol. This preparation can be kept in the ice-box for two weeks without deteriorating. The average dose was 30 cc. daily. This preparation was readily taken as a rule by the patients without untoward symptoms.

The outstanding effects were a rapid gain in body weight and improvement in muscle strength. This gain in weight was most striking in the emaciated patients, and furthermore ceased when it reached approximately the normal weight of the patient before the onset of the disease. Associated with the improvement of muscle strength there occurred in the asthenic patients with hypotension a progressive rise in blood pressure to about the normal level, where it remained.

Concomitant with the increase in body weight there occurred a temporary rise in heat production. This increase in metabolism with relatively slight remissions was found to persist as long as three months after medication was stopped without any fall in weight. In an attempt to lower the heightened metabolic rate we subsequently exposed five of the patients to x-ray treatment. Three of these showed a drop to normal and have been active and well since. Of the other two, one has had a subtotal thyroidectomy performed and showed only a temporary postoperative drop, plus 40 to plus 20 per cent, followed by a rise to almost the previous level (plus 30 per cent). The other patient has been fairly active but still shows high metabolism (plus 39 per cent) in spite of the x-ray treatments.

Another effect, a source of great relief to the patient, was the influence upon abnormal menstruation which is a common accompaniment of Graves' disease. Seven of the women complained of severe dysmenorrhea. In each of these we observed

a very decided improvement in this distressing symptom. In one subject with prolonged bleeding time and who showed purpuric spots over the body and had menstrual hemorrhages so profuse as to necessitate on one previous occasion a blood transfusion, we observed an arrest of the hemorrhages with decrease in bleeding time from 8 to 4 minutes and disappearance of the purpura. On three different occasions this patient showed return of all these symptoms following cessation of the feedings, and each time we observed alleviation of the symptoms following the resumption of interrenal gland administration. In two other cases we likewise observed reappearance of the dysmenorrhea following discontinuance of the interrenal feedings and also subsequent disappearance of the symptoms after the feedings were resumed.

Diarrhea was a common symptom and usually disappeared at the same time that improvement in general condition occurred. One patient had severe chronic diarrhea, averaging about 20 bowel movements daily. This condition was gradually controlled following interrenal emulsion feedings. It reappeared following cessation of feedings and was again controlled on three different occasions since her discharge from the hospital following oral administration of ox interrenal emulsion.

Four cases illustrative of the group will be described briefly.

*Case I:* A housemaid, 16 years of age, complained of enlargement of the neck, increased nervousness and excessive perspiration, for about one month. Her appetite had been increasing since the onset of these symptoms. Menstruation commenced at 14, occurred every 28 days, lasted 4 days, and was regular and painless.

*Status:* She showed flushed face, questionable exophthalmos, symmetrically enlarged thyroid, fine tremor of fingers, and moist warm palms. The heart was not enlarged; there were no murmurs and the rate was 96. The blood pressure was 145-90; the weight, 56.8 kg. The basal metabolic rate was plus 24 per cent. The urine was negative for sugar and albumin. The blood count showed 36 per cent lymphocytes.

She received 30 cc. daily of a 50 per cent emulsion. Two weeks later her pulse was 78, blood pressure 130-80, and weight 57.7 kg. Her basal metabolism dropped to plus 3 per cent. We continued the feedings two weeks longer, or one month in all, after which she showed a further increase in weight to 59 kg.; the pulse remained about 70 per minute; the blood pressure was 120-80. The flushed appearance of her face was no longer observed. She seemed well, was working and active. She was seen at irregular intervals for the next four months. There was no reappearance of her symptoms. Her thyroid had decreased in size and was only slightly enlarged.

*Case II:* A girl, 19 years of age, bookkeeper, was admitted to Montefiore Hospital, March 7, 1922. During 1918, at the age of 15, the patient developed thyroid enlargement which receded following

the administration of iodine. She then started to menstruate. In 1920 her neck again enlarged, and at the same time she commenced to lose weight and to tire easily. She was given large doses of an iodine containing preparation following which she continued to lose weight more rapidly and to grow progressively weaker. She complained of palpitation, excessive perspiration and increased prominence of her eyes. Her menstruation gradually lessened in amount and became very painful. The month before admission there was amenorrhea.

*Status:* The patient was an emaciated young girl, extremely nervous, tossing about in bed, with choreaform movements and marked bilateral exophthalmos. She was bedridden and weighed 39 kg. The thyroid was large, symmetrical and very firm in consistency (iodine involution); thrill and bruit were present over it but there was no expansile pulsation. The heart was enlarged; the rate was 144 and there was a systolic murmur over the precordium. Marked throbbing of vessels of neck was observed. There was a fine tremor of the fingers, wasting of muscles and asthenia. The urine showed a trace of sugar. There was incontinence of urine and feces. Basal metabolic rate was plus 47 per cent; the blood pressure, 140-75.

The patient was kept in bed for two weeks. The pulse remained about 140; there was slight lessening of her nervousness. Basal metabolism was plus 46 per cent; the weight remained 39.0 kg. Following this, she took 30 cc. of glycerol emulsion of ox interrenal glands daily. Within two weeks there was slight increase in weight and a rise in metabolism to plus 70 per cent. After about one month her weight increased to 44.5 kg. and the metabolic rate was plus 58 per cent. After ten weeks of feeding with this emulsion she showed a total gain of 11 kg. Her basal metabolism was plus 52 per cent. There was no change in the pulse rate, which averaged 120 throughout. There was a marked improvement in muscle strength, so that the patient was able to climb a flight of stairs with little distress. At the same time that this improvement occurred the thyroid increased in size (from 36 cm. to 38 cm. neck circumference) and became softer in consistency. There was considerable new growth of scalp and axillary hair, very slight improvement in exophthalmos and disappearance of glycosuria. During the next month the patient showed no changes except a further increase in weight. X-ray treatments of the thyroid area were then started. She received four exposures in the next three months. There was a drop in metabolism to plus 31 per cent and return of menstruation. The patient returned to her home and resumed her work. She reported for observation seven months later, at which time her basal metabolism was minus 6 per cent; her weight, 59.1 kg.; her pulse, 84, and blood pressure, 115-85. The urine was negative for sugar and albumin. She was active and apparently well. Her exophthalmos was still definitely present. Menstruation was normal and regular. The thyroid was still definitely enlarged, soft in consistency, no bruit or thrill being present. We attempted to produce further reduction of the thyroid by administration of minute doses of desiccated thyroid and iodine. However, the patient was still sensitive to these and consequently the attempt was abandoned.

*Case III:* A housewife, married, 38 years of age, was admitted to Montefiore Hospital on April 5, 1922. Onset of her illness dated back to about a year and one-half previous to admission. The patient commenced to lose weight and to grow very weak. She had lost 55 pounds up to the time she entered the hospital. Menstruation had commenced at 14 years and occurred every 28 days, lasting 4 days. Since onset of the present illness it had become irregular and very

painful. Upon admission she had become so weak that she was scarcely able to stand.

*Status:* The subject showed an anxious expression and mild exophthalmos; the skin hung loosely, significant of loss of much weight, and was warm and moist. The thyroid was symmetrically enlarged and firm in consistency; loud bruit and thrill were present and throbbing of the neck vessels. The heart was enlarged; the rate was 130; there was loud systolic over the precordium, accentuated second aortic and very severe myasthenia out of proportion to all other symptoms. The blood pressure was 170-75; blood count showed 39 per cent lymphocytes. The urine contained a trace of sugar. Her weight was 66.3 kg., and basal metabolic rate was plus 70 per cent.

The patient was kept in bed and given full diet and mild sedatives. She remained in the hospital one month, during which time we attempted to feed her glycerol emulsion of ox interrenal, but owing to its fleshy odor the patient refused medication. We did not attempt to administer this again during her stay. There was loss in weight from 66.3 to 63.6 kg.; her basal metabolic rate remained between plus 70 and plus 74 per cent; her pulse remained between 105 and 130; the blood pressure dropped slightly to 160-90.

She then returned home, where she remained in bed owing to her weakness. She returned for observation on May 18, about a week after she left the hospital. The pulse was 106, the weight was 61.8 kg., and basal metabolism plus 68 per cent. On June 12 she developed auricular fibrillation and signs of cardiac decompensation, including cyanosis, dyspnoea and rales over the bases of both lungs. Digitalis was administered. After one week the acute cardiac upset was controlled. Her heart rate averaged 120, with an occasional extra systole. On this day we started administration of glycerol emulsion of ox interrenal glands, 45 cc. daily. This time she retained this preparation without any untoward symptoms. Within two weeks she was well enough to come to the hospital again for a basal metabolic rate determination. Her heart was regular, averaging 96 beats per minute, and the blood pressure was 145-85. Her weight increased to 66.3 kg. There was a sharp rise in metabolism to plus 103 per cent. We continued the administration of interrenal emulsion and also of digitalis. Three weeks later her pulse remained about 90 and was regular. She showed definite improvement in muscle strength so that she was able to carry on her housework to a limited degree. Her weight increased to 70.4 kg. Her metabolism had dropped to plus 79 per cent. She was seen again after an interval of three weeks. Her pulse rate remained unchanged. Her weight was 68.6 kg. and her basal metabolic rate was plus 68 per cent. We then discontinued the interrenal feedings and one month later started X-ray treatments, giving her four exposures during the next three months. Her metabolism showed only a slight drop, averaging plus 56 per cent. Her weight remained at 75 kg. Her pulse averaged about 96. In spite of her high metabolism she was active and fairly comfortable. Observation made 9 months later showed a drop in metabolism to plus 16 per cent and a gain in weight to 81.4 kg. Four months subsequent to that, however, her B. M. R. had risen to plus 55 per cent again. Her weight dropped to 72.3 kg. and she seemed worse as compared with the last observation. On May 15, 1924, she again reported to the hospital. Her weight was 82 kg.; pulse, 80; B. M. R., plus 39 per cent. She feels well, is active and does her housework. Her thyroid remains symmetrically enlarged. The bruit, however, is no longer heard. She is still somewhat nervous and excitable and still shows slight exophthalmos.

*Case IV:* A high school student, 19 years of age, was admitted to Montefiore Hospital on May 29, 1922. During the summer of 1919 she noticed that she tired very easily. She later complained of frequent palpitation of the heart and excessive perspiration and nervousness. Her weight was 59 kg. She rested most of the summer and there was slight improvement of symptoms. Subsequently she developed enlargement of the thyroid and exophthalmos. At the same time her weight had dropped to 50.4 kg. on admission. Menstruation commenced at 13, was irregular, painful, and since onset of the present illness, profuse.

*Status:* The nourishment was fair; the patient appeared excited and nervous. Moderate bilateral exophthalmos and large diseased tonsils were noted. There was a symmetrically enlarged thyroid, soft in consistency; thrill and bruit were present. There was throbbing of the neck vessels. The heart was not enlarged; the rate was 110 and regular; a faint systolic murmur was heard over the base. The blood pressure was 125-60. Tremor of the fingers was present; the palms were moist and warm. Muscle strength was fair. The basal metabolic rate was plus 30 per cent.

The patient was put to bed on full diet and mild sedatives for one week. After this time there was no change in weight; the pulse averaged 100 to 110. There was troublesome diarrhea since admission which did not abate during this period. She then received 30 cc. daily of glycerol emulsion of ox interrenal. During the following week there was a profuse painful menstruation. Her pulse averaged 96; blood pressure, 110-65; basal metabolic rate, plus 30 per cent; diarrhea gradually lessened. There was a gain in weight to 53.1 kg. After three weeks she showed a total gain of 4.1 kg. and a rise in metabolism to plus 39 per cent. Her pulse averaged 90; the blood pressure was 110-80, and diarrhea was controlled. Tonsillectomy was then performed under local anesthesia. She left the hospital on July 20. At that time her pulse averaged between 80 and 85. The blood pressure was 115-80; weight, 55.4 kg., and basal metabolic rate, plus 28 per cent. All subjective symptoms except occasional palpitation of heart abated. Exophthalmos which was mild receded. Menstruation was slightly painful but no longer profuse. Muscle strength was good. One month later she returned for observation. Since she left hospital she had remained at home, fairly active, feeling well, taking emulsion daily. Her weight was 55.9 kg., the pulse 95, and basal metabolic rate plus 31 per cent. The following menstruation was normal. At this time administration of interrenal emulsion was discontinued. The patient was given 5 X-ray treatments during the next four months, during which there was bradycardia of 54 beats per minute, increase in weight to 61.3 kg. and fall in basal metabolism to minus 18 per cent. One month later metabolism was plus 1 per cent; weight, 59.5 kg.; bradycardia persisted 54 beats per minute. Electrocardiograph showed sino-auricular block, L. V. P., sinus, arrhythmia, and bradycardia. This condition has persisted to the present day. The patient is now a school teacher, active, and feels well. The pulse is still slightly irregular, menstruation is normal, and exophthalmos is no longer present. Thyroid gland is palpable and firm in consistency; no bruit or thrill present. The blood pressure is 120-80, and the basal metabolism is normal.

#### DISCUSSION

Marine and Leuhart in 1911 collected data showing that the conception that Graves' disease is a thyroid disease is untenable.



Their conclusion at that time was: "The essential physiological disturbance in the thyroid in exophthalmic goiter is a relative insufficiency, its reaction compensatory and its significance symptomatic." The facts that sufficient injury to interrenal function (as developed by Golyakowski, Marine and Baumann, and by Scott) leads to a chronic increase in heat production and that removal of the thyroid prevents it are undoubtedly of great importance as regards the etiology of exophthalmic goiter. We believe that this is the nearest approach to the experimental production of Graves' disease in animals that has yet been obtained. Indeed, the clinical manifestations of acute cases of Graves' disease are almost identical with the clinical manifestations produced in rabbits and cats by sufficient but sublethal suppression of interrenal function as shown in the following table:

INTERRENAL INSUFFICIENCY	GRAVES' DISEASE
(a) Increased B.M.R. (usually) Associated with increased appetite.	(a) Increased B.M.R. (usually) Associated with increased appetite
(b) Thyroid hyperplasia.	(b) Thyroid hyperplasia.
(c) Lymphoid hypertrophy	(c) Lymphoid hypertrophy
1. Thymic enlargement	1. Thymic enlargement
2. General lymphoid enlargement (hypertrophy)	2. General lymphoid enlargement (hypertrophy)
(d) Asthenia	(d) Asthenia
(e) Increased sexual activity	(e) Increased sexual activity (abnormal menstruation)
(f) Hypersensitiveness	(f) Hypersensitiveness
1. Toxins	1. Toxins (acute intercurrent infections)
2. Drugs	2. Drugs (epinephrin)
(g) Increased peristalsis	(g) Increased peristalsis

Marine and Baumann pointed out that this conception of exophthalmic goiter would explain the continued lymphoid and thyroid stimulation as in part dependent upon weakness or exhaustion of the interrenal glands associated with normal or increased functional activity of the chromaffin tissue. These authors are careful to state that while interrenal injury alone or combined with increased epinephrin discharge represents two of the essential alterations from which many of the disturbed interrelations directly or indirectly arise, they do not believe that they will fully explain exophthalmic goiter.

The principal clinical phenomena which we have observed to be beneficially affected following the oral administration of

glycerol emulsion of ox interrenal glands in cases of Graves' disease were as follows:

1. Asthenia.
2. Dysmenorrhea.
3. Diarrhea.
4. Body nutrition.
5. Heat production.
6. Tachycardia.
7. Blood pressure.

Asthenia is one of the most constant clinical manifestations of Graves' disease. It is an additional expression of the insufficiency shown by these patients in the transformation of energy into work, which has recently been emphasized by Boothby and Plummer. It is the most prominent clinical symptom of states in which, in our opinion, interrenal insufficiency plays a fundamental role, notably exophthalmic goiter, Addison's disease, status thymicolymphaticus and status thymicus, experimentally produced by bilateral suprarenalectomy. On the other hand, in contrast with this, let me emphasize that we observed striking improvement in asthenia and what we have interpreted as increased efficiency, both in storage and utilization of energy following feedings with interrenal gland emulsion. We believe that the interrenal gland contains a substance capable of restoring to the cell its capacity to perform such functions more efficiently. These effects have not been observed with the dried preparations that we have tried up to the present time, with the possible exception of acetone extracted glands. Furthermore, we believe that the effects observed are the manifestations of only infinitesimal traces that have escaped destruction in preparation and through digestion. These manifestations are, therefore, only glimpses of what may be realized when these substances are concentrated and prepared so that they may be introduced parenterally. This has been classically illustrated in the differences in their respective actions observed between oral and parenteral administration of other hormones such as epinephrin, insulin and the growth-producing principle of the anterior pituitary. In thousands of feeding experiments Uhlenhuth and others have obtained in a few instances glimpses of growth acceleration, whereas Evans has shown that this effect can invariably be pro-

duced in white rats by the intraperitoneal injections of a preparation of anterior pituitary.

The improvement that we have observed in disturbances accompanying menstruation, chiefly pain and excessive hemorrhage, also deserves emphasis. We believe that this influence upon ovarian activity is accomplished through the close functional relation that exists between the ovaries and the interrenal glands.

We have seen in ten instances a gradual fall in basal metabolism and pulse rate after a preliminary rise to within normal limits within 3 to 4 months after the interrenal feedings were stopped. In three of these cases x-ray treatments of the thyroid area were given during that interval. However, in two other instances the patients had received without relief Roentgen ray treatment of the thyroid area before administration and showed definite improvement after interrenal feedings. It is our impression that those three subjects showing the decrease in metabolism and pulse rate after x-ray treatment were destined to show these changes anyway, but that they may have been accelerated by the x-ray exposures. Some of our patients have shown decrease in heat production following the oral administration of interrenal emulsion and without any x-ray treatments.

In conclusion I wish to point out that evidence is rapidly accumulating that the interrenal glands exert an inhibitory or regulatory control over the thyroid and that a functional interrenal insufficiency plays a fundamental role in the development of Graves' disease. In a series of twenty cases we have uniformly observed beneficial effects, notably rapid increase in body weight and concomitant improvement in muscle strength following the oral administration of glycerol emulsion of ox interrenal glands.

#### CASE I.

<i>Date</i>	<i>Pulse</i>	<i>Weight</i>	<i>B.M.R.</i>	<i>Remarks</i>
1-5-22	96	56.8 Kg.	+24%	Started Interrenal Emulsion
1-19	78	57.7 Kg.	+ 3%	
1-31	80	59.0 Kg.	— 2%	Stopped Interrenal Emulsion
2-28	76	59.0 Kg.	— 6%	
3-30	70	59.0 Kg.	— 6%	
6-22	74	59.0 Kg.	— 1%	

## CASE II.

<i>Date</i>	<i>Pulse</i>	<i>Weight</i>	<i>B.M.R.</i>	<i>Remarks</i>
3-9-22	144	39.0 Kg.	+47%	
3-14	136	39.0 Kg.	+46%	Started Interrenal Feedings
3-21	124	38.1 Kg.	+62%	
3-28	120	39.5 Kg.	+70%	
4-11	120	40.0 Kg.	+63%	
4-27	124	44.5 Kg.	+58%	
5-9	120	48.1 Kg.	+58%	
5-16	114	47.9 Kg.	+45%	
5-23	124	49.3 Kg.	+52%	
5-31	130	50.0 Kg.	+54%	X-ray treatment, 6-24, 7-8
7-13	114	53.1 Kg.	+39%	Stopped Interrenal Feedings
8-15	110	53.4 Kg.	+42%	X-ray treatment, 7-24, 8-24
11-9	108	53.1 Kg.	+31%	X-ray treatment, 11-21
7-26-23	84	59.0 Kg.	— 6%	
11-3	80	60.5 Kg.		

## CASE III.

<i>Date</i>	<i>Pulse</i>	<i>Weight</i>	<i>B.M.R.</i>	<i>Remarks</i>
4-18-22	130	66.3 Kg.	+70%	
4-27	105	65.4 Kg.	+76%	
5-9	120	63.6 Kg.	+74%	
5-18	106	61.8 Kg.	+68%	Started Interrenal Feedings
6-29	96	66.3 Kg.	+103%	6-19
7-18	90	70.4 Kg.	+79%	
8-8	90	68.6 Kg.	+68%	Stopped Interrenal Feedings
10-31	96	70.0 Kg.	+62%	X-ray treatment, 9-11, 10-5
12-14	96	75.0 Kg.	+56%	10-26, 11-23
9-13-23	89	81.4 Kg.	+16%	
1-29-24	108	72.3 Kg.	+55%	
5-15-24	80	82.0 Kg.	+39%	

## CASE IV.

<i>Date</i>	<i>Pulse</i>	<i>Weight</i>	<i>B.M.R.</i>	<i>Remarks</i>
6-6-22	110	50.4 Kg.	+30%	Started Interrenal Feedings
6-13	96	53.1 Kg.	+30%	
6-27	90	54.5 Kg.	+39%	
7-18	84	55.4 Kg.	+28%	X-ray treatment, 7-22, 8-14
8-17	95	55.9 Kg.	+31%	X-ray treatment, 9-11, 10-10
				11-18

9-30	90	56.8 Kg.	.	Stopped Interrenal Feedings
11-7	54	60.9 Kg.	—16%	
11-16	42	61.3 Kg.	—18%	
12-17	54	59.5 Kg.	+ 1%	
1-19-23	54	59.0 Kg.	+ 1%	
10-13	54	54.0 Kg.	— 3%	
1-4-24	60	55.0 Kg.		
4-26	54	55.0 Kg.		

## DISCUSSION OF PAPER OF DR. SHAPIRO

Dr. Walter Timme, New York: I would like to ask Dr. Shapiro how the emulsion of the cortex is prepared and where the extract is obtained.

Dr. Shapiro, New York City: By an arrangement that we have with the veterinarians in a slaughter house in New York City, we are able to obtain the glands immediately after their removal from the oxen. The method of preparation consists of carefully freeing the glands of fat and then splitting them sagittally. The medulla is carefully dissected out and the remaining cortical portion is then hashed and emulsified with glycerol.

# Editorial

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## BIBLIOGRAPHIES

To one who is not conversant with the routine of an editorial office it would perhaps come as a surprise to learn how much unedifying labor is required to insure satisfactory bibliographic work. Taken by and large, even with much expenditure of time upon the part of editors, satisfactory results are by no means always achieved. In case of books, no little slipshod work is tolerated by even excellent publishing houses. Some of the difficulties have been admirably expressed by the Editor of the *Journal of Radiology* in the May, 1924, issue (page 168).

"An editorial writer in a recent medical publication notes with pained surprise." it is stated, "what has long been an annoying and glaring fault in the great majority of American medical writers, namely, such a lack of accuracy in bibliographies as to render them a source of much wrath to anyone attempting to look up the literature to which they refer. It is rare to find that a bibliography has been carefully and accurately checked by the author or by some one else competent to do it. Frequently the author jots down his references inaccurately; sometimes it is even worse than this, and he exhibits a total lack of knowledge as to what a complete citation should include.

"Recently the writer witnessed an author checking a bibliography appended to the manuscript of a really worth-while book which he was about to have published. The bibliography was long, the author was weary with an unaccustomed and uninteresting task, a task much lightened for him, however, by the services (free gratis) of an excellent medical librarian. Several times the librarian remarked of a book, 'Edition so and so,' or of an author's name, 'Initials so and so,' only to be met with the reply, 'Oh, that does not matter.' In citing the page, volume, month and year of a reference to a periodical she was told sev-

eral times that the learned doctor cared not at all for one or the other of these items, he seemed quite satisfied if he had either the volume or the year. It never entered his head that many times, through some slip of the stenographer or the proof-reader, the volume number becomes most useful as a check upon the year, and vice versa, nor that the page number might save the reader's looking through the index of the volume referred to and thus save some busy doctor's time, to say nothing of his patience.

"Such carelessness is inexcusable, but it is often met. Only the librarian and the man who does his own literary research has any idea of the waste of time and the annoyance so caused. Anywhere from five minutes to half a day may be required to run down a reference. True, it is not often that the reference is needed badly enough to spend a half day searching for it, but sometimes it is. Another editorial writer recounts just such an experience. In looking up a certain bibliographic reference he traced it through five articles before he found the article to which the bibliography referred, for it was not original with B, to whom A's bibliography referred, nor yet with C, to whom B referred, nor to D, to whom C referred, nor yet with E, but its father was finally discovered in the person of F. Rather an extreme instance, but not a medical librarian in the country who does not have such an experience time and time again.

"As the writer first referred to says: 'It is an imposition upon readers to present to them a list of references to the literature of a subject, only to have them discover after an annoying search that many of the references are incorrect, that some of the articles cannot be found, and that others have no bearing upon the subject.'

"Such slovenliness is a reflection upon American scholarship and often dims its brilliancy in the eyes of our more careful colleagues across the seas."

A besetting sin of Americans is rushing madly toward some goal, often with little probability that the goal is worth the strain. It is not fair, however, that in such strenuousness writers should carelessly add to the existing confusion in the medical literature.—R. G. H.

## Book Reviews

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LECTURES ON ENDOCRINOLOGY. Walter Timme, Paul B. Hoeber, Inc., New York, 1924. Pp. 123, 8°.

This little book is frankly a verbatim reprint of an article published by the author in the periodical literature in 1921. As such it, of course, takes no cognizance of much interesting work that has appeared since that date, and its restricted size precludes detailed consideration of most of the earlier work. One gathers the impression that the lectures are of interest primarily as setting forth the working theories of an alert clinician confronted with a somewhat bewildering array of constitutional anomalies with which he feels constrained to attempt to deal helpfully. The book is written in a delightfully entertaining style.—R. G. H.

THE HUMAN TESTIS AND ITS DISEASES. Max Thorek. J. B. Lippincott Co., Philadelphia and London, 1924. Pp. 548, 8°.

In this comprehensive work the author has brought together for the first time in a single volume in the English language a large proportion of the available data on the anatomy, physiology, pathology, diseases and therapeutics of the testis. Much emphasis is laid on the endocrine aspects of these topics. In addition to summaries of the work of others the author has incorporated the results of several years of personal study on the experimental and clinical phases of the subject. The book is well illustrated and is attractively printed.

In general, the literature has been judiciously treated, though, as is inevitable in such a work, readers will differ as regards evaluation of specific contributions. The more conservative readers will regret the statement that "the endocrine doctrine teaches that character and mentality are not merely influenced by, but are the accurate and actual expressions of our secretions." This is an example of the sort of facile hokum from which the author has mostly steered clear.

The work would have been somewhat improved by more careful attention to elementary grammar and spelling. Sequence of tenses is not infrequently ignored; in a single line on page 179 "arthropods" and "tritons" are misspelled. Such defects are, however, not numerous. The author occasionally lapses into undue exuberance of style, as on page 75. The most serious criticism of the work is that the bibliographic material is left



in a deplorably shipshod form: the citations are lacking in uniformity and the references are often incomplete. Altogether, however, the book is one that will be welcomed by endocrinologists the world over. It will be found both instructive and entertaining.—R. G. H.

THE PARATHYROID GLANDS IN RELATION TO DISEASE. H. W. C. Vines, London: Arnold, 1924. Pp. 118. Figures 10. Price 10s 6d.

Reviewed in *Physiol. Abst.*, 1924, 9, 148.

# Abstract Department

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Increase of adrenin action by amino-acids (Weiterer Beitrag zur Kenntnis der Wirkungssteigerung von Adrenalin durch Aminosäuren). Abderhalden (E.) & Gellhorn (E.), Arch. f. d. ges. Physiol. (Berl.), 1924, 203, 42-56.

Amino-acids so increase the action of adrenin on heart-strips that the minimal effective concentration is reduced to one-tenth. The effect is produced by d- and l-alanine, d- and l-leucine, d- and l-tyrosine, 3,5-di-iodo-tyrosine, l-histidine, and l-cystine, and also by beta-alanine. It is so far specific that amino-acids do not affect the action of other positive inotropic active agents as calcium and strontium chlorides. The lowering of temperature following intraperitoneal injection of adrenin into white mice is increased by addition of amino-acids.—A. T. C.

Castration and adrenals (Kastration und Nebennieren). Altenburger (H.), Arch. f. d. ges. Physiol. (Berl.), 1924, 202, 668-669.

White mice, castrated at 3 weeks, showed three months later enlargement of the adrenal cortex and diminution of the medulla. The widening of the cortex equally involves the three zones.

—A. T. C.

The action of adrenalin on human digestion (L'azione dell' adrenalina sulla digestione gastrica dell' uomo). Bindi (N.), Gazz. d. osp. (Milano), 1922, 43, 197-199.

Berti and Biavedoni's method is used. With 1 mg. of adrenalin Bindi observed some acceleration of functions. He therefore believes it to be a strong stimulant of the splanchnics which are said to determine the more active motor functions.—P. M. N.

Genito suprarenal syndrome (suprarenal virilism) in a girl one and a half years old, with successful operation. Collett (A.), Am. J. Dis. Child. (Chgo.), 1924, 27, 204-218.

Family and personal history were normal until 9 months of age, when the patient had whooping cough. Abnormal growth of hair developed prior to this. Two months later she had an attack of bronchitis and convulsions. The child became plump, heavy, with rather a large head and general physical overgrowth; the vocal cords were unusually long and broad. Mentally she was quicker and cleverer than children of corresponding age. There was marked growth of hair on labia majora and mons veneris, on thighs, shoul-

der and back; there was no axillary hair. The genitals showed a well developed labia majora and mons veneris with a penis-like organ in place of the clitoris; hymen and uterus were normal. A tumor was felt on the left side under the costal margin. This was operated on and found to be a typical hypernephroma of rather long standing. Because of the infiltration with lime, the author considers that it was of early origin. When seen a year later, the child was more child-like in her appearance; all abnormal growth of hair had disappeared; there was less fat on the body and the genitals had somewhat receded in size. The author claims that this is the first case to be reported of a child who had survived removal of a tumor for a genito-suprarenal syndrome.—M. B. G.

A quantitative color reaction given by adrenalin and urine. Friend (H.), J. Biol. Chem. (Balt.), 1923, 57, 497-505.

The color reaction given by pure solutions of adrenalin with sulfanilic and nitrous acids is quantitatively proportional to the adrenalin concentration. The reaction is no longer given after the adrenalin has been treated with ferric chloride. None of the urinary constituents tested has given a positive reaction before ferric chloride and a negative reaction after it. It appears possible that the urinary constituent giving the color reaction before, but not after the ferric chloride treatment, is adrenalin. Values for urinary adrenalin determined according to the method outlined in the paper are given for a number of pathological cases, including several of diabetes.—F. S. H.

Carbon dioxide and adrenaline as regulating factors for the musculature of the bronchi and pulmonary vessels. Magnus (R.), Brit. Ass. Adv. Sc. Rep., 1923, 478-479.

Experiments on surviving perfused cat lungs show that the bronchio-spasm produced by defibrinated or hirudinized blood is relaxed by the addition of 1.4-30% carbon dioxide to the air respired. Carbon dioxide in concentrations from 1.4% up causes in most cases constriction of the lung vessels, but when adrenalin is present in the blood in amounts over 1 part in a billion the effect of carbon dioxide is to cause dilatation. Changes in the concentration of O and N in the blood have no influence on the bronchial or vascular tone. It is concluded that carbon dioxide in physiological concentrations tends to maintain the air passage normal and in the presence of physiological amounts of adrenalin to facilitate pulmonary circulation. An increased alveolar carbon dioxide tension may, under pathological conditions, also have an important regulating influence.—Chem Abst., 18, 1522.

Clinical studies in Addison's disease. Rowntree (L. G.), Tr. Ass. Am. Physicians, 1924, Atlantic City, May 6 & 7.

In the last 4 years we have had 21 cases of Addison's disease. Four patients received no treatment and died within a month; 5 received some form of organotherapy; 12 received full treatment and died despite the treatment; 5 showed very good results. Two recent cases cannot be fully reported on. We do not feel that influenza can be excluded from casual relationship. There was tuberculosis in 8 cases. Syphilis, malaria, typhoid fever, trauma and pregnancy, also played a part. Renal function showed very slow excretion of water. The blood plasma fell within normal limits. The blood does not flow readily. Lymphocytosis was a common occurrence. Liver function seemed to be normal. The basal metabolism was studied in 13 cases, and 8 were within normal limits; 4 were below normal. The breathing was very slow, with heavy sighing. The patient complained of cramps after taking suprarenal preparations, so the most recent method is to give preparations of the suprarenal cortex, which does not cause cramps to any extent. Pigmentation is usually increased in patients who do not improve under treatment. The treatment can combat functional insufficiency only of the suprarenal glands, but the treatment probably exerts no influence on the fundamental underlying factors; but results warrant giving the method a fair trial. The results of treatment depend on the patient's tolerance. In some instances an actual intolerance exists. In the shocklike crises we have given shock treatment first. Some patients can take 5 minims, some can take 20; the hypodermic administration causes less cramps than the oral method.—J. Am. M. Ass., 82, 1886.

**Suprarenal virilism.** Scabell (A.), *Deutsche Ztschr. f. Chir. (Leipz.)*, 1924, 185, 1-46.

Scabell compares with 2 cases he describes 23 from the literature in which pseudohermaphroditism was associated with hyperplasia of the suprarenals, and 47 cases of precocious puberty, or virilism with acquired suprarenal hyperplasia. Hypoplasia of the bone marrow was a frequent finding, and was conspicuous in his 2 personal cases. In the first, the girl had been normal to the age of 12, when virilism developed, with a suprarenal tumor, which proved fatal in 3 years. In the other case hyperplasia of the suprarenals was associated with false female hermaphroditism. Scabell discusses suprarenal hypergenitalism in the congenital, acquired and rudimentary forms, with special regard to pathologic constitutions.—J. Am. M. Ass., 82, 2092.

**Experimental observations on the adrenals and the chromaffin system.** Wislocki (G. B.) & Crowe (S. J.), *Johns Hopkins Hosp. Bull. (Balt.)*, 1924, 35, 187-193.

Adrenal insufficiency was produced in dogs by the combined surgical removal of a part of the adrenal glands and implantation

of radium in the remainder. The radium produced an area of necrosis which gradually destroyed the adrenal tissue. The medulla of the adrenals and the abdominal chromaffin body were destroyed in the dog without producing symptoms. A fragment of cortex amounting to about one-fifth of the total cortex was found to be necessary for the maintenance of life. After removal of all the cortex, the animals died with a terminal fall in blood pressure and temperature. If the cortex as well as the chromaffin system produces epinephrine, this fact would not explain the death of animals after extirpation of the cortex.—R. G. H.

The function of the carotid gland (*Über die Function der Carotid-drüse*). Fischer (W.), *Ztschr. f. d. ges. exper. Med. (Berl.)*, 1924, **39**, 477-486.

Investigations on kittens. Extirpation of the carotid bifurcation, together with the whole of the sessile gland on both sides (in a period of 6 to 20 days with 2 operations). As controls, kittens from the same litter were used. The consequences of the extirpation do not appear until after about 6 weeks, beginning with reduced liveliness, diminished appetite and playfulness, diffuse alopecia, inactivity of the extremities, backwardness in growth, retarded dentition, protruding abdomen, cachexia, spleen atrophy; the bones are porous, rough, having little calcareous content. The synchondrosis of the bones is widened by irregular zones of petrification. The suprarenal glands and epithelial bodies show a characteristic hypertrophy. The carotid gland has, apart from the function of the chromophile system, functions which are of importance to growth and development of bone.—*Physiol. Abst.*, **9**, 183.

Paget's disease and hyperspasmodic paraplegia in flexion (*Maladie osseuse de Paget et paraplégie hyperspasmodique en flexion*). Ardin-Delteil, Azoulay (R.) & Lagrot, *Bull. et mém. Soc. med. d. hosp. d. Par.*, 1923, **47**, 920-924.

No definite syndrome of glandular or polyglandular disturbance was found in this case of Paget's disease. The injection of 2 mg. of adrenaline produced no noticeable reaction. The injection of 0.05 of hypophysis extract raised the blood pressure in 20 minutes from 19-10 to 20-11.—F. S. H.

Insulin-like substances (*Ueber insulinartige Körper. I.*). Brugsch (T.) & Horsters (H.), *Biochem. Ztschr. (Berl.)*, 1924, **147**, 150-162.

Extract of thyroid gland in one case caused a slight lowering of the blood sugar in the rabbit. In two other instances it was ineffective. A slight depressant action of parathyroid extracts is reported. Extract of the adrenals gave the characteristic rise. Liver extract was followed by a rise in blood sugar. When a watery solution of an alcoholic extract of spleen was administered there oc-

curred a fall in blood sugar which persisted for some time. Placenta extract acted similarly and was found to be quite toxic to rabbits. Yeast, salts of phosphoric acids and arsenic acids caused lowering of blood sugar. An extract of pancreas was ineffective. Insulin seemed to stimulate bile secretion.—F. S. H.

**Endocrine dysfunction as a possible etiologic factor in progressive deafness.** Drury (D. W.), Boston M. & S. J., 1924, 190, 1029-1033.

The author points to the ovary, pituitary and thyroid as glands possibly having an influence in progressive deafness. He bases this suggestion on the observation that in the 44 subjects he studied, 25 showed evidence of endocrine disturbances.—J. C. D.

**Obesity.** Faber (E. E.), Ugesk. f. Laeger (Copenhagen), 1923, 85, 105-109 (Feb. 15).

Faber explains how the physiologic balance requires that the calory content of the food must equal the basal metabolism plus the work of digestion, plus the amount of energy used up in muscular work. He expresses this in the equation  $C = B + D + M$ . War experiences and research since have confirmed the view that the intake of calories is often above the physiologic requirement, and the superfluous calories throw an extra task on the organs which regulate oxidation and radiation of heat. If they are unequal to this task, the superfluous nourishment is deposited as fat. The metabolic anomaly in this endogenous obesity may not affect the basal metabolism, but thyroid treatment may stimulate the organs involved and lead to the throwing off of the fat deposits. Another point he emphasizes is that the organs involved (endocrine glands) may become exhausted from their extra work, so that even when the intake of calories is reduced very low they still are unable to cope with them. Obesity is rare in the young because their endocrine glands are so active that they can handle excess of work. In exophthalmic goiter the abnormally active thyroid diverts the energy to tremor and sweating rather than to accumulation of fat. The tendency to accumulation of fat increases as the endocrine system grows less active with advancing years. This is especially manifest in women at the menopause although the basal metabolism is normal. He remarks in conclusion that even the most pronounced cases of endogenous adiposity may show no benefit from thyroid or other treatment until the intake of food is materially reduced. This confirms the almost invariable blending of the endogenous and exogenous types.—J. Am. M. Ass., 80, 1496.

**Practical notes on endocrine therapy** (Note pratiche di terapia endocrina). Fubini (E.), Rassegna di clin., terap. [etc.] (Roma), 1924, 23, 61-73.

According to the author, glycerin extracts are preferable to dry preparations, and in pluriglandular disturbances each glandular substance should be administered separately in order not to destroy any of the incretory activities. Anaphylactic syndromes, hemoclastic autogenous crises, adrenal insufficiency and cases of osteomalacia have been successfully treated.—P. M. N.

**The influence of the ovary and the thyroid on the regeneration of white and red blood cells** (Beiträge zur Physiologie der Drüsen. L. Asher. Experimentelle Untersuchungen über den Einfluss der Drüsen mit innerer Sekretion auf die Wachstumsvorgänge, zugleich Beiträge zum Konstitutionsproblem. I.) Furuya (K.), Biochem. Ztschr. (Berl.), 1924, 147, 390-409.

Moderate loss of blood from thyroidectomized rabbits causes a slowing of the regeneration of the blood elements which is greater than that in ovariectomized animals. Moderate hemorrhage produces a definite increase in the polymorphonuclear count of normal rabbits and a relative decrease in the leucocytes. This alteration is less in degree in animals from which the ovaries have been removed and is lacking in thyroidectomized rabbits. These responses are taken as evidence for the belief that the ovary and thyroid exert an influence on the growth processes of the blood tissue and a similar though quantitatively different effect on bone marrow.—F. S. H.

**The dependence of phagocytosis on internal secretion. A new method for the study of internal secretions.** (Beiträge zur Physiologie der Drüsen. L. Asher. Experimentelle Untersuchungen über den Einfluss der Drüsen mit innerer Sekretion auf die Wachstumsvorgänge, zugleich Beiträge zum Konstitutionsproblem. II.) Furuya (K.), Biochem. Ztschr. (Berl.), 1924, 147, 410-424.

Hamburger's method for the study of phagocytic activity was used. It was found that the removal of the ovaries reduced the phagocytic activity of leucocytes toward carbon particles. Thyroid removal acted similarly but to a greater degree. The serum of thyroidless rabbits reduced the phagocytic power of normal exudate cells. The serum of ovariectomized animals had a like but lesser action. The phagocytic activity of cells from ovariectomized rabbits was also reduced by serum from thyroidless animals. Feeding thyroid substance to thyroidless animals raised the phagocytic power of the leucocytes to practically normal values. The same is true of feeding with ovary.—F. S. H.

**Endocrinology from physician's point of view.** Gow (A. E.), Brit. M. J. (Lond.), 1924, i. 697-700.

Gow is of the opinion that the majority of extracts of ductless glands, as at present prepared, have no obvious effect administered by mouth. Animal experiment has shown that tissue extracts in

general, when injected intravenously, have much the same effect as any other foreign protein, and, with few exceptions, are in no way specific. There is no evidence that any extract other than thyroid or parathyroid is absorbed as such from the alimentary tract. However, epinephrin is valuable in shock, in asthma and other spasmodic affections such as cardiospasm, urticaria and angioneurotic edema, and pituitary extract is a stimulant to a failing myocardium, especially in toxic myocarditis and in the third stage of labor. Gow states emphatically that if any advance in therapeutics is to be made with glandular extracts of doubtful action the practice of giving multiple extracts as a sort of blunderbuss, in the hope that one among the many may hit the mark, must be checked.—J. Am. M. Ass., 82, 1895.

**Influence of abnormal external temperatures on thyroids and testes** (Beiträge zur biologischen Bedeutung der innersekretorischen Organe. II. Der Einfluss abnormer Aussentemperaturen auf Schilddrüse und Hoden), Hart (C.), Arch. f. d. ges. Physiol. (Berl.), 1922, 196, 151-176.

House-mice, kept at 32°-40° C. for some days showed marked atrophy of the thyroid, with disappearance (sometimes almost complete) of colloid, marked degeneration of the spermatozoa-forming epithelium and complete cessation of spermatozoa production in the testes. When they were kept at 4°-7° C. there was increased thyroid function, colloid-packed follicles, and marked secretion-vacuoles in the cuboidal epithelium, while active spermatogenesis was visible in sections of the testes.—A. T. C.

**A preliminary note on the properties of an alleged erythropoietic hormone.** Leake (C. D.) & Bacon (F. J.), J. Pharmacol. & Exper. Therap. (Balt.), 1924, 23, 353-363.

Desiccated spleen and red bone marrow combined in equal proportions by weight contain, on the average, 2.4 mgm. of water-soluble iron per gram, and 28.9 mgm. of lecithin-phosphatids per gram. Unless these substances represent integral components of the physiologically active agents in desiccated spleen and marrow, it is doubtful whether they can be considered much of a factor in the erythropoietic effects observed after the administration of spleen-marrow compound. In spleen and red bone marrow, erythropoietic agents are found which (a) withstand desiccation; (b) are thermostable at 100° Centigrade; (c) are water-soluble; (d) are inactivated by alcohol and ether; (e) are capable of oral administration; (f) are capable of biological assay; (g) do not deteriorate on standing in sterile solution, and (h) have no untoward accessory actions.

—R. G. H.

**The purins of the blood and the influence of the incretory glands**  
(Le purine del sangue e l'influenza su di esse delle glandole a



secrezione interna). Lovaglio (R.), *Folia med.* (Napoli), 1924, 10, 296-306.

Splenectomy increases and thyroidectomy diminishes blood purins. Extirpation of the parathyroids probably is more important in this connection than that of the thyroid. The adrenals and gonads have but little influence.—P. M. N.

Changes in blood sugar (*Ueber die Veränderungen des Blutzuckers*. I.). Nakahayshi (S.) & Abelin (J.), *Biochem. Ztschr.* (Berl.), 1924, 147, 544-556.

Studies on sheep and rabbits showed that a diminution of glycogen in the liver and hyperglycemia are not always accompanied by an increased sugar utilization. When thyroid is fed, the liver becomes almost glycogen free, but no increase in the respiratory quotient obtains. Also after adrenalin injection, in spite of glycogen mobilization and hyperglycemia and increase in gaseous exchange, there is only an insignificant increase in sugar oxidation. It was found that thyroid feeding induces no alteration in the behavior of the blood sugar. Before and after thyroid ingestion, as usual, the polarimeter value of the blood is less than that of the reduction value. The polarization value increases with time. After adrenalin injection there does occur a change in the blood sugar in that the polarization value becomes greater than the reducing value. It decreases on standing.—F. S. H.

Investigation concerning the influence of thyroid and ovarian treatment upon the development and the appearance of the feathers in birds (ducks) [*Recherches concernant l'influence du traitement thyroïdien et ovarien sur le développement et l'aspect du plumage chez les Oiseaux (Canards)*]. Parhon (C. I.) & Parhon (C.), *Compt. rend. Soc. de biol.* (Par.), 1923, 80, 683-686.

Feeding thyroid to ducks 4 to 5 days old results in a retardation of growth and a delay in the growth of plumage. Feeding ovary had no appreciable effect.—T. C. B.

Chemical therapeutic agents and opotherapy (*Les agents thérapeutiques chimiques et l'opothérapie*). Pierrett (R.), *Bull. gén. de thérap.* [etc.] (Par.), 1924, 175, 114-126.

Review.—F. S. H.

Internal secretion and gaseous exchange of blood. Yamakita (M.), *Tohoku J. Exper. Med.* (Sendai), 1922, 3, 567-607.

The O loss of normal non-nucleated red corpuscles stored in the ice chest at 4° to 7° ranges from 50 to 80 per cent in 70 to 80 hours, but if mixed with adrenaline the O loss ranges from 15 to 40 per cent in the same time. If stored in the incubator at 34° to 38° the loss of O is 80 to 100 per cent in 15 to 50 hours, but in the

presence of adrenaline the decrease is 50 to 60 per cent. Generally the influence of adrenaline on carbon dioxid production is greater than on O consumption. In blood with or without adrenaline, O consumption and carbon dioxid production do not run closely parallel to each other; even after the entire loss of O the production of carbon dioxid can continue. Adrenaline has no influence on the O capacity of the blood. When the blood is hemolyzed the time taken for complete reduction is shortened, and by storage in the incubator for 10 hours the O is entirely lost, while if adrenaline is added the reduction of blood is retarded and is nearly the same as that for non-hemolyzed normal blood. Adrenaline has no relation to the serum, cell membrane, cell structure or stroma of the red corpuscles. The inhibitory action of adrenaline solution on the gaseous metabolism of blood is not due to chloretone contained in it, nor is it due to its acidity. HCl of the same acidity increases the rate of reduction of blood. Adrenaline also retards the rate of reduction of blood when it is treated with reducing gas. When the blood is reduced with carbon dioxid gas the effect is more marked than when nitrogen gas is used. Adrenaline does not accelerate the rate of oxidation but has a tendency to retard it. For a few minutes after the intravenous injection of adrenaline, just during the rise of the blood pressure, the blood of the external jugular vein is red-colored and contains nearly as much O as arterial blood. This action of adrenaline has no relation to the state of the blood flow. If blood is taken, within a few minutes after the intravenous injection of adrenaline, the gaseous exchange in vitro is much decreased. By the direct inhibitory action of adrenaline on the reduction of oxy-hemoglobin the O supply to tissues and organs is disturbed, and there may occur anoxemia, which is further increased by constriction of the blood vessels. The inhibitory effect of adrenaline on the gaseous exchange of blood has no relation to white corpuscles, blood platelets or fibrin. Adrenaline and asphyxia produce many similar effects and phenomena in the body; some of the phenomena are explained by the anoxemia provoked by it. Pituitrin and thyro-protein have no similar effect on the gaseous metabolism in vivo or in vitro.—Chem. Abst., 17, 2152.

**Ovigenesis during sexual maturity.** Allen (E.), *Am. J. Anat.* (Phila.), 1923, 31, 439-481.

Carefully wrought line of evidence based upon experiments in white mice. The concept that the ova are differentiated in the ovary shortly after birth, or at least before the attainment of puberty, requiring that they remain dormant for long periods, is questioned. Allen holds that a cyclic proliferation of the germinal epithelium gives rise to a new addition of young ova to the cortex of the adult ovary at each normal oestrous period. An average of from 400 to 500 young ova may differentiate in one ovary at each period, while an average of  $4\frac{1}{2}$  ova of an earlier generation mature. The per-

**The effect of the placenta on menstruation.** Jacoby (A.), N. York M. J. & Med. Rec. (N. Y.), 1923, 115, 619.

In order to test the theory that the internal secretory action of the placenta depresses the ovary and its allies, the authors administered placental extract in 5 gr. doses regularly three times a day for at least three months in a series of 25 cases in which menorrhagia was a prominent symptom. Four showed no change in menstrual function; the other 21 all showed a noticeable diminution of the amount of blood lost and the duration of the flow was usually reduced. The discomfort and pain during menstruation was considerably lessened in many instances. The blood pressure during the taking of the placental extract usually fell about 10 mm. No ill effects were reported from prolonged taking of this extract except in a few instances in which nausea and vomiting occurred. In spite of the small series, the large preponderance of successful cases lends encouragement to the view that the secretion of the placenta is effective in controlling the hyperactivity of the ovary and the glands aiding it in its function.—Am. J. Obst. & Gynec., 7, 754.

**Hormone sterilization of female animals (Ueber hormonale Sterilisierung weiblicher Tiere).** Knaus (H.), Arch. f. d. ges. Physiol. (Berl.), 1924, 203, 394-396.

Positive results were obtained in rats by repeated injections of corpus luteum extracts. The after litters were larger than usual (in three cases 19, 15 and 9), attributed to the delayed ripening of the follicles affected by the treatment.—A. T. C.

**Experimental testicle transplants (Hodenverpflanzung in Tierexperimenten).** Kurtzahn (H.), Arch. f. klin. Chir. (Berl.), 1923, 126, 536.

These experiments, carried out on dogs, were partly transplants of portions of testicle into muscle, peritoneum, and so on, and partly injections of testicular substance by a paraffin syringe into similar tissues and into spleen and liver. These latter seem to succeed even better than direct implantations, but the final result in all alike is disappointing. The author concludes that both auto- and homo-transplants in the dog always necrose; the peripheral parts of a mass last longer than the central, but the spermatogenous elements quickly disappear. When implanted by injection, the tissue has relatively a longer life but terminates in absorption. As there is no reason to think that grafts succeed better in man than in the dog, it appears that the good results claimed clinically for such grafts, if they have any organic basis at all, owe it to absorption of the tissue. If employed at all, transplantation by means of injection presents these advantages: substitution of a simple injection for a definite "operation"; elimination of infection; notably diminished damage to the host-tissue; good apposition and well-nourished sur-

face contacts; more rapid absorption of the necrosed portions; elimination of suggestion. Intramuscular injection is the best.

—Med. Sc., 10, 317.

Can Steinach's doctrine concerning the function of the Leydig cells be considered as proof? (Ist Steinach's Lehre von der Funktion der Leydig'schen Zellen zwingend?). Kyrle (J.), Med. Klin. (Berl.), 1921, 17, 1018, 1050-1052.

The author believes, in opposition to Steinach, that the interstitial cells of the testes are a "trophic auxiliary organ" for the incretory canalicular epithelium. The interstitial cells grow exuberantly and tend to regenerate after injury of the canalicular epithelium if a certain quantity of canalicular epithelium cells remain. There are remains of canaliculi even in cryptorchid testicles. When the epithelium of the canaliculi regenerates the interstitial cells degenerate again. The interstitial cells also make use of the superfluous nutritive material which was originally destined for the canaliculi, and deliver it again into the blood as a kind of incretion. After hematotoxic injury of the testicle (alcoholism, etc.) the interstitial cells do not grow because they are injured also. The interstitial cells are scanty before puberty and increase only with the beginning of spermatogenesis. During active spermatogenesis the Leydig cells decrease. The author has observed in the atrophic testicle of a four-year-old boy a group of perfectly developed canaliculi surrounded by Leydig cells and he believes that the canaliculi developed under the protective influence of accumulated interstitial cells. Ligation of the vas deferens causes augmentation of the interstitial cells only if the vessels are also injured. If the whole testicle is in a state of inferiority and reduced vitality vasoligation sometimes causes temporary rejuvenation.—A. B.

Interstitial cells in the testis of the rabbit after unilateral castration (Über die Menge des Zwischengewebes im Hoden des Kaninchens nach einseitiger Kastration). Lipschütz (A.) & Ibrus (A.), Skandin. Arch. f. Physiol. (Leipz.), 1923, 44, 237-247.

Unilateral castration in the young rabbit did not bring about any change in the relative mass of Leydig cells or their proportion to the total weight of the testicle 2½ to 14 months after operation.

—G. E. B.

Effect of ovariectomy and lutein injections on behavior of rats. Macht (D. I.) & Seago (D. W.), J. Comp. Psychol. (Balt.), 1924, 4, 151-163.

The effect of ovariectomy and of injections of corpus luteum extracts was studied by Macht and Seago on the behavior of albino rats in the circular maze. Extirpation of both ovaries produced a distinct impairment in the muscular activity and general behavior

of the rats. Injections of small doses of ovarian extract, and more particularly of corpus luteum extracts, produced a distinct improvement in the running time and the cerebrospinal efficiency of both normal and ovariectomized rats, which improvement was noticeable soon after injection and was still present on the following day.

—J. Am. M. Ass., 83, 66.

**An ovarian graft; a case report.** Miller (C. J.), N. Orl. M. & S. J., 1924, 76, 547-548.

An ovarian isograft became swollen and painful and the patient developed metrorrhagia. The graft was removed. One end was cystic, the cyst containing about 100 cc. of clear fluid. An "active" corpus luteum was also found. Within a few days after removal of the graft the metrorrhagia ceased.—R. G. H.

**Hermaphroditism in a 10-year-old subject** [Hermaphroditismus (verus) glandularis alterans bei einem 10 jährigen Individuum]. Sand (K.), Skandin. Arch. f. Physiol. (Berl. u. Leipz.), 1923, 44, 59-75.

Report of a subject 10 years old, brought up as a boy but showing at different times characteristics of male and female. Surgical exploration with histological examination of fragments taken from the gonads showed an ovary on one side and testis on the other.

—G. E. B.

**Influence of the adrenals and ovaries upon precocious secondary sexual development.** Siegel (A. E.), Arch. Pediat. (N. Y.), 1924, 41, 265-272.

Two cases in girls are described to show that different glandular pathology may bring about a different yet somewhat related picture. One case is of a girl, 8 years of age, who died of general sarcomatosis after the removal of a sarcoma of the right ovary. She showed premature development of the secondary sexual characteristics, such as marked development of the mammae and the presence of labial genital hair. She was not massive or tall for her age. The other girl, 3 years of age, died of encephalitis and infective nephritis. She was large for her age, massive in her bony structure and in muscular development, her head was large and striking, leonine; the hair on the head was abundant. The genitalia were large and the pubic hair unusually developed. Autopsy showed a small suprarenal tumor of the right side which presumably was responsible for the precocious sexual development but which was not a factor in the production of death.—M. B. G.

**The action of mammary gland extracts on the circulatory system and a study of their activity in animals** (Azione degli estratti mammarî sul sistema circolatorio, e contributo alla conoscenza

del loro meccanismo d' azione nell' organismo animale). Spirito (F.), *Rassegna di clin., terap. [etc.]* (Roma), 1924, 23, 31-41.

From physiological and clinical experimentation the author concludes that the activity of the mammary glands is due only to their endocrine relations with the adrenals and the gonads. The direct action on muscle and uterine vessels and on the circulatory system in general he believes to be insufficient in intensity and duration to produce any great effect.—P. M. N.

A case of massive hypertrophy of the breasts in a young girl. Wright (T.), *Bull. Buffalo Gen. Hosp.*, 1924, 2, 31.

Wright reports a typical case of puberty hypertrophy of the breasts, and calls attention to the fact that it may be due to an endocrine imbalance, whereby the normal inhibitory influence to mammary hypertrophy fails to act at the proper time.

—Am. J. Dis. Child., 27, 652.

Preliminary report of a case of mixed sex. An apparent male, with a testis in scrotum on right side; ovary, tube and uterus in inguinal canal on left side. Young (H. H.), *Johns Hopkins Hosp. Bull. (Balt.)*, 1924, 35, 165-168.

The case is reported of an individual operated upon for removal of a mass, supposedly an undescended testicle, in the inguinal canal. The mass proved to consist of an ovary, uterus and Fallopian tube. On the opposite side was found in the scrotum a testicle, somewhat undeveloped (as shown by microscopic examination). Psychologically, the subject was normally masculine. The penis was normal in size, but with congenital chordee. The urinary meatus was a cleft in the scrotum. Hair growth and distribution were normally masculine. It is stated that this is the first human case of true lateral glandular hermaphroditism recorded. Unlike all the lateral hermaphrodites found in animals, this patient was masculine externally, though he had inactive tubules and a functioning ovary. The interstitial cells were, however, apparently hyperplastic and no well developed lutein cells were seen.—R. G. H.

Case of dystrophia adiposogenitalis in a child two years of age, with results of seven months' treatment. Boyd (C. S.), *Arch. Pediat. (N. Y.)*, 1923, 40, 736-746.

This boy was marasmic until 18 months of age. When first seen by the author at the age of 2 years he presented a typical picture of Froelich syndrome with some signs of hypothyroidism. Under intensive treatment, consisting of whole pituitary substances and thyroid, he improved to a great extent, the improvement being more pronounced in those symptoms which were due to hypothyroidism and to a lesser extent in those due to dyspituitarism.

—M. B. G.

Two cases of diabetes insipidus cured by injections of extract of the posterior lobe of the hypophysis (*Deux cas de diabète insipide guéri par les injections d' extrait de lobe postérieur d'hypophyse*). Denechau (D.) & Mandroux (J.), *Bull. et mém. Soc. méd. hôp. de Par.*, 1924, 48, 561-566.—F. S. H.

A "forme fruste" of dystrophia adiposogenitalis and its experimental allocation (*Ueber eine Forme fruste der Dystrophia adiposogenitalis und ihre experimentelle Begründung*). Dietrich (H. A.), *Ztschr. f. Geburtsh. u. Gynäk. (Stuttg.)*, 1924, 87, 146-156.

In cases of "forme fruste" dystrophia adiposogenitalis 1 cc. of adrenalin produces an abnormal type of blood sugar curve during the first hour after administration. The first reaction is a fall. This is followed by a rise.—F. S. H.

Biological tests of hypophysis extracts: action on the crest of the cock (*I saggi biologici degli estratti di ipofisi: azione sulla cresta del gallo*). Di Mattel (P.), *Riv. osp. (Roma)*, 1924, 14, 105-118.

A criticism of the methods of standardization of hypophysis extract. The author proposes as a practical, constant and sufficiently exact test cyanosis of the crest and wing of the cock. He advises endovenous application of 0.0025 gm. fresh posterior lobe in the wing. The reaction is completed in about an hour, and in 3 hours the same animal can be experimented on again. The cock is very resistant to large doses.—P. M. N.

Tumor of the hypophyseal stalk. Fraser (J.), *Edinb. M. J.*, 1924, 31.

Fraser showed a case of developmental tumor of the hypophyseal stalk in a girl, aged 9 years. The symptoms were adiposity, squint, headache, and deterioration of vision. The roentgenogram revealed a calcified, partly cystic epithelial tumor of the stalk, producing a deficiency of the anterior lobe, with Frölich's syndrome, also interruption of the right optic tract with irritation of the third cranial nerve and an increase in intracranial tension. The only suitable treatment in this case seemed to be decompression, which was done, with considerable improvement resulting.

—*Am. J. Dis. Child.*, 28, 112.

The influence of pituitrin on diuresis (*Zur Kenntnis der Pituitrinwirkung auf die Diurese*). Molitor (H.) & Pick (E. P.), *Arch. f. exper. Path. u. Pharmakol. (Leipz.)*, 1924, 101, 169-197.

Experiments were made on dogs with a bladder fistula, and the excretion of urine was studied after administration of 250 cc. of water by mouth. Subcutaneous injections of small doses of pituitary extract suppressed diuresis, whether given before or after

the excretion of this water began. In no case was increased diuresis observed. The anti-diuretic action was observed in dogs with Eck-fistula, and was not affected by inhalation of amyl nitrite, injection of ergotamine, sodium nitrite, papaverine, phlorhizin, nitroglycerin, caffeine, or thyroid extract. The effect does not appear to be produced, therefore, by vascular changes, especially as it lasts for many hours, whereas the vascular effects of pituitary are fleeting. The failure of thyroid extract to restart a diuresis stopped by pituitary is interesting in view of Eppinger's demonstration of the value of thyroid administration in edema. Injection or oral administration of urea and hypertonic salts will, however, restart a diuresis.—*Physiol. Abst.*, 9, 134.

Hypophyseal extract and diuresis (Azione dell'estratto ipofisario sulla diuresi nella pratica infantile). Misasi (M.), *Pediatria* (Napoli), 1922, 30, 819-822.

Pituitrin in normal children causes concentration of the urine sooner than in adults. The chlorides increase in direct ratio with the specific gravity. In kidney diseases concentration is not obtained so soon; the urine remains concentrated longer and the chlorides diminish. In atrophy no variation in the specific gravity is obtained.—G. V.

Influence of diet on insulin action (Ueber den Einfluss der Ernährung auf die Wirkung des Insulins). Abderhalden (E.) & Wertheimer (E.), *Arch. f. d. ges. Physiol.* (Berl.), 1924, 203, 438-442.

Rats fed chiefly on a fat diet do not show the typical hypoglycemic convulsions following injection of insulin. Rats fed chiefly on protein also are unaffected, though animals on mixed fat-protein-carbohydrate diet are affected as usual. Rats in the convulsion stage show a rectal temperature of 23° or less. Animals fed fat or protein do not show such low temperatures. In these animals three times the lethal dose of insulin scarcely produces any symptoms. Frogs are very resistant. Twenty units injected into the dorsal lymph sac of a 53 gram frog produced no marked symptoms. Pigeons and guinea-pigs show a similarly great resistance.

—A. T. C.

Functioning of the fetal pancreas after ablation of the maternal pancreas (Fonctionnement du pancréas foetal apres ablation du pancréas maternel). Aron (M.), Stulz (E.) & Simon (R.), *Compt. rend. Soc. de biol.* (Par.), 1923, 89, 571-573.

In the absence of the maternal pancreas, before the islands of Langerhans begin to function in the fetus, mother and fetus present hyperglycemia. After development of the islands the mother presents hyperglycemia, while the fetus is protected. .

—T. C. B.



An insulin-like material in various tissues of the normal and diabetic animal. Best (C. H.), Smith (R. G.) & Scott (D. A.), *Am. J. Physiol.* (Balt.), 1924, 68, 161-182.

Insulin is present in various tissues other than the pancreas. It is present in reduced amounts in completely depancreatized dogs.

—T. C. B.

Preliminary report on the effect of insulin on the rate of heat production and its significance in regard to the calorogenic action of adrenalin. Boothby (W. M.) & Wilder (R. M.), *Med. Clin. N. Am.* (Phila.), 1923, 7, 53-56.

This is a report on the results of 4 experiments on the effect of insulin on the rate of heat production of one normal person and three diabetic patients under standard postabsorptive basal conditions. It is determined by these observations that insulin is not a calorogenic agent like thyroxin with a delayed reaction, nor, probably, does it in itself possess an immediate calorogenic action like adrenalin.—I. B.

Studies of intermediary carbohydrate metabolism and insulin. I.

Studies on normal animals (*Studien über intermediären Kohlenhydratumsatz und Insulin. I. Versuche an Normaltieren*). Brugsch (T.), Benatt (A.), Horsters (H.) & Katz (R.), *Biochem. Ztschr.* (Berl.), 1924, 147, 117-149.

Studies of the respiratory exchange are insufficient to determine the mechanism of the action of insulin; studies of the intermediary metabolism of the carbohydrates are necessary. To this end a method was devised by which the intermediary processes in the liver, muscles and other organs could be studied immediately after death. The method consists in suspending the finely divided tissues in aerated, sugar-containing Ringer's solution. Observations were made on normal animals, animals which had been fasted for 24 hours and animals in which hypoglycemia had been produced by insulin. The course of the intermediary changes was followed by determinations of the glycogen content of the organs, the formation and disappearance of glucose with or without the formation of lactic acid, the formation of hexose phosphoric acid and intermediate products. It was found that the normal liver forms only glucose and a bit of lactic acid; that the liver from fasted animals changes glucose to lactic acid, and that after insulin poisoning there occurs a marked glucose deficit along with the formation of hexose phosphoric acid and intermediary sugars. From this it is apparent that insulin effect is in the nature of an activation of an oxidizing-synthesizing process in liver and muscle. Insulin is not simply a neutralizing antagonist of the liver diastase, but is an antagonizing synergist.—F. S. H.

A method of titration of insulin (*Sur un mode de titration de l'insuline*). Desgrez (A.), Bierry (H.) & Rathery (F.), *Bull. gén. de thérap. (etc.)* (Par.), 1924, 175, 97-102.

Dissatisfied with the physiological assay of insulin as an index of its efficacy in diabetes, as based on the "rabbit-unit," the authors proposed that the substance be evaluated on the basis of dry weight of preparation as a purified and sterile powder. The standard of such preparation should be that the injection of 5 mg. per kilo body weight into a dog fasted for 24 hours produces during the ensuing 2 hours a 40 to 50% lowering of the arterial blood-sugar.

—F. S. H.

The effect of insulin on the oxygen and carbon dioxide tensions in air between the skin and the muscles. Campbell (J. A.) & Dudley (H. W.), *J. Physiol. (Lond.)*, 1924, 58, 348-354.

The curve for oxygen tension in air injected under the skin follows the blood sugar after insulin. There is an increase of carbon dioxide tension also, lasting an hour or two.—T. C. B.

Action of insulin (*Sur quelques modalités d'action de l'insuline*). Desgrez (A.), Bierry (H.) & Rathery (F.), *Compt. rend. Soc. de biol. (Par.)*, 1923, 80, 473-475.

Animals react differently to the same dose of insulin. Variations of hypoglycemia in the same animal are not proportional to the dose of insulin. Liquid extracts cause a toxicity which is independent of the hypoglycemic effect. There is an individual optimal dose, beyond which no advantage is gained.—T. C. B.

Influence of insulin on the vasoconstriction of the liver (*Zur Wirkungsweise des Insulin als Vasokonstriktion der Lebergefäße*). Freund (E.), *Wien. klin. Wchnschr.*, 1923, 36, 528-529.

More than 10 years ago the author demonstrated that ether and alcoholic substances could be isolated from the pancreas which caused marked vasoconstriction in the surviving liver of the dog. Extracts of muscle and testicle did not produce this constriction. When the liver was perfused with Ringer's solution and insulin was added the rapidity of perfusion sank markedly. Insulin, therefore, produces vasoconstriction of the liver and increases the resorptive power of the liver cell. This does not prevent insulin from having other properties also.—J. K.

The behavior of the blood lipoids after fat feeding in normal and diabetic subjects with and without the administration of insulin (*Ueber das Verhalten der Blutlipide unmittelbar nach Fettzufuhr bei normalen und zuckerkranken Menschen, mit und ohne Anwendung von Insulin*). Hartmann (H. U.), *Biochem. Ztschr. (Berl.)*, 1924, 140, 307-317.

The administration of glucose causes no change in the total lipid content of the blood. When 50 grams of butter and 20 grams of cereal are fed to normal and diabetic subjects the lipoids of the blood increase during the first hour and then gradually fall back to the fasting level within the succeeding 4 hours. When insulin (50 units) is given one hour before the fat feeding it may be followed by a tendency to a decline in the total lipid content of the blood; when the test meal is then given one hour after the insulin the total lipid content of the blood usually increases as after the test meal not preceded by insulin.—F. S. H.

**Action of insulin. I. Sugar formation in the surviving frog liver** (Beiträge zur Wirkung des Insulins. I. Zuckerbildung der überlebenden Froschlber), v. Issekutz (B.), *Biochem. Ztschr.* (Berl.), 1924, 147, 264-274.

When insulin is added to the perfusion fluid it fails to influence sugar formation by the surviving liver of the frog. If, on the other hand, the frog has been treated the day before with insulin its liver shows a decrease in sugar-forming ability of from 20 to 25 per cent, and reacts less to adrenalin.—F. S. H.

**The effect of insulin on the phosphoric esters in blood and muscle.** Kay (H. D.) & Robinson (R.), *Chem. & Industry Rev.*, 1924, 43, 313.

During an investigation of the action of the phosphoric esterase shown to be present in bone on the acid-soluble phosphorus compounds in blood, muscles, and other tissues, it was found that the amount of organically bound phosphate contained in rabbit muscle, which is readily hydrolysed by this enzyme, was increased by 15-25% above the normal when insulin had been previously injected and the animal was killed at or just before the onset of convulsions. Similar results were obtained by estimating the increase of inorganic phosphate in the muscle extracts after autolysis, as in Embden's "lactacidogen" determination. Assuming that the conclusion arrived at by Embden and his collaborators, that the lactacidogen of muscle is a hexose phosphoric ester is correct, the discovery of a definite increase in this substance after insulin affords a probable explanation of the fate of the sugar which disappears from the blood and which, it is known, is neither transformed into glycogen nor fat. The increase actually found would account for about three times the amount of sugar which disappears from the blood, but in this calculation no allowance is made for any mobilization of sugar from glycogen or other reserves. These results agree with those just published in abstract by Wagner and Andova, who, using a slightly different method, find about the same increase in "lactacidogen" after insulin.

—Chem. Abst., 18, 218.

Radiographic study of arterial lesions in diabetics (*Les lésions artérielles des diabétiques décelées par la radiographie*). Labbé (M.) & Lenfantin (H.), *Bull. et mém. Soc. méd. d. hôp. de Par.*, 1924, 48, 522, 524.

Radiography is found to be of help in determining the extent of arterial lesions in diabetics. The opacity is assumed to be due to deposition of calcium salts.—F. S. H.

The skin reaction to tuberculin in diabetes (*La cuti-réaction à la tuberculine chez les diabétiques*). Labbé (M.) & Boulin (R.), *Bull. et mém. Soc. méd. d. hôp. de Par.*, 1924, 48, 701-702.

From tests on 12 diabetics and 12 controls it is concluded that diabetes leads to an attenuation of the usual reaction to tuberculin.  
— F. S. H.

Some variations in the acid-base balance of the blood in disease. Myers (V. C.) & Booher (L. E.), *J. Biol. Chem. (Balt.)*, 1924, 59, 699-712.

The uncompensated acidosis of severe diabetes promptly responds to the administration of insulin as indicated by the rise in plasma pH and bicarbonate.—F. S. H.

Insulin and phlorhizin diabetes. Nash (T. P.), *J. Biol. Chem. (Balt.)*, 1923, 58, 453-462.

Fasting female dogs were used. They were phlorhizinized and then treated with insulin. There was a marked diminution in nitrogen excretion following the administration of insulin. Either a specific retention of nitrogen or a protein sparing action has been produced. The latter interpretation is favored. Sugar was withdrawn from the blood under the influence of insulin and consequently the sugar excretion in the urine was lowered. On the other hand, this lowered excretion was followed by an increase which indicates to Nash that the sugar so withdrawn was surrendered to the blood again. These findings are taken as corroboration of the view of Benedict and Nash that phlorhizin effects an intrinsic impairment of utilization of sugar by the tissues.—F. S. H.

The value of insulin in the utilization of carbohydrates. Olmsted (W. H.) & Kahn (S. H.) with the assistance of Case (Eleanor) & Taussig (Nan), *Boston M. & S. J.*, 1924, 190, 1018-1028.

Thirteen cases of diabetes were studied to determine whether there is any relation between the amount of insulin given and the amount of carbohydrate utilized. The authors concluded from their results, which are given very fully in a series of tables, that (1) "It is possible to demonstrate under the conditions outlined a quantitative relationship between insulin administered and carbohydrate

tolerated, one unit of 'H' insulin being equivalent to 1.4 grams of carbohydrate; (2) in the majority of diabetics, sugar derived from protein shows the same quantitative relationship to insulin as that derived from starch. Of the 9 diabetics on whom feeding excess of protein was studied, 3 showed very disastrous effects."—J. C. D.

The technic of blood-sugar estimation as done at the Memorial Hospital of Philadelphia. Petty (O. H.) & Sherrill (W. P.), *Internat. Clin. (Phila.)*, 1923, 3 (series 33), 22-28.

After returning to their homes following insulin treatment, most patients require periodical blood-sugar examinations. As many patients live at a considerable distance from a well-equipped laboratory, Petty and Sherrill chose the Benedict modification of the Lewis-Benedict method of blood-sugar estimation because the picrate solution employed acts as a preservative preventing glycolysis during transportation of the specimen. A description of the taking of the blood from the patient at a distance from the hospital, as well as the technic of the blood-sugar determination, constitutes the major portion of this article.—I. B.

Blood sugar regulation and its importance in the pathogenesis of diabetes mellitus (Ueber Blutzuckerregulation und ihre Bedeutung für die Pathogenese des Diabetes mellitus). Pollak (L.), *Med. Klin. (Berl.)*, 1921, 17, 925-930.

The blood-sugar level is kept constant by a nervous hormone regulation mechanism. A hormone irritation of the blood can cause sugar excretion from the liver. Adrenalin does not seem, therefore, to be a physiological factor in blood-sugar regulation. The blood acidity caused by lactic acid which is produced in the muscles is said to excite the liver to mobilize sugar, but the liver mobilizes sugar even if no acidification takes place and if the sugar is utilized only for building up tissues. The author supposes that every digression of the blood-sugar level over or under the normal causes activity of the regulation mechanism. This level remains almost normal in phlorizin diabetes even after paralyzing the sympathetic ends by ergotoxin. Temporary sinking of the sugar level excites the liver to mobilize more sugar; temporary rising tends to cause sugar consumption. Hyperglycemia also checks sugar production in the tissues. Intravenously administered glucose (35 gr.) disappears from the blood in 15 minutes. Cardial and nephritic transudations have the same sugar level as the blood. Nearly all kinds of hyperglycemia, with the exception of diabetes mellitus, depend on nervous central or peripheral irritations. The parasympathetic system has almost no influence. The nervous system is not a necessary factor in blood-sugar regulation, but the liver and the entire endocrine apparatus are. After extirpation of the adrenals the blood sugar sinks and disappears completely, but it may be in-

creased again by piqure, and the capability to mobilize sugar is not lost. The blood-sugar level in diabetes mellitus is high and of pathological lability, depending on diet, muscle activity, etc. In diabetes mellitus there is probably no decreased capability to consume sugar within the tissues (isolated organs of depancreatized animals consume sugar normally) but there is no irritation by the pancreas hormone causing sugar consumption. Even the capability of the liver to produce glycogen is not altered. The transformation of glycogen into sugar within the liver is increased in diabetes mellitus and is the most essential factor of it. The liver of depancreatized animals delivers abnormally much sugar into a perfusing liquid, not in consequence of nervous irritation, but of an alteration of the blood sugar regulation. There is decreased reaction of the liver upon variation of the blood-sugar level. Nephrectomy in a depancreatized dog causes the blood sugar to rise; phlorizin has the opposite effect, while in the normal animal a constant level is conserved. The sugar production in the liver of depancreatized animals may be increased by piqure and adrenalin or decreased by opium, etc. The production of amino, keto and fat acids, which act similarly to adrenalin, incites the hypersensitive diabetic liver to mobilize glycogen. Albumin has a similar effect. Sugar oxidation and glycogen production are thus not primarily altered in diabetes mellitus, but there is an alteration of their regulation. In diabetes mellitus there is not properly, therefore, an alteration of carbohydrate metabolism.—A. B.

The influence of lack of sleep on assimilation of sugar (Beiträge zur Diabetesforschung. VI. Mitt. Über den Einfluss des Schlafmangels auf die Zuckerassimilation). Sakaguchi (K.) & Asakawa (O.), Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo, 1922, 28, 515-526; abst., Ber. ü. d. ges. Physiol. (Berl.), 1923, 18, 82.

The blood-sugar curve was established in healthy and in diabetic subjects after administration of equal amounts of carbohydrates and other foodstuffs, both after a good normal sleep and after a sleepless night. It was shown that neither sleeplessness nor mental strain reduced the tolerance for carbohydrates of healthy or of diabetic subjects.—R. G. H.

Treatment of diabetics with low threshold of sugar elimination (Beiträge zur Diabetesforschung. VII. Mitt. Über die Behandlung von Zuckerkranken mit niedriger Zuckerausscheidungsschwelle). Sakaguchi (K.), Asakawa (O.) & Ueda (H.), Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo, 1922, 29, 179-203; abst., Ber. ü. d. ges. Physiol. (Berl.), 1923, 18, 82.

Diabetic subjects have been described in whom the urine was sugar-free, but in whom small amounts of sugar (under 1%) would appear in the urine on administration of 50 to 100 gm. of rice.

According to Bang, the excretion of sugar takes place only if the blood sugar reaches a height of 0.12 to 0.14%. It is therefore treated as a very low threshold of sugar elimination, yet the author assumes that it is not a question of renal diabetes since in a fasting condition the urine is sugar-free. In such cases, glycosuria has no harmful influence on carbohydrate tolerance. Strict dietary limitation is therefore unnecessary and may even become harmful. The author believes that in such cases not only should the sugar elimination be considered, but also the threshold of sugar elimination.—R. G. H.

**Ketosis and carbohydrate metabolism.** Shaffer (P. A.), *Ann. Clin. Med. (Balt.)*, 1924, 3, 93-95.

A brief summary of Shaffer's conception of ketogenic balance. Carbohydrate is used both for fuel and for supplying an intermediate product in the oxidation of fats. When the latter process fails ketone bodies appear in the urine. Fats are therefore "ketogenic." Carbohydrate, similarly, in that it aids in complete oxidation of fats, is "antiketogenic." Glycosuria without diacetic acid in the urine shows that the carbohydrate tolerance is lower than the carbohydrate ingested but is not so low as to provide a negative ketogenic balance. If there is both sugar and diacetic acid in the urine the carbohydrate tolerance is so low that, at the rate of that subject's total metabolism—the rate at which the subject is living—a ketogenic balance cannot be maintained, and anything that disturbs it further may produce a marked acidosis and coma. The danger line is crossed. The patient should be in bed and probably will need insulin. If, on the other hand, there is ketosis without glycosuria it probably means merely that the glucose or carbohydrate supply is insufficient to provide a ketogenic balance and that that is not due to a lowered carbohydrate tolerance.—R. G. H.

**Glycolysis in bloods of normal subjects and of diabetic patients.** Tolstoi (E.), *J. Biol. Chem. (Balt.)*, 1924, 60, 69-75.

The glycolytic power of 8 normal subjects and 11 diabetics was studied. Some of the bloods were studied both at room temperature and at 37° C. Aseptic precautions were used and the red and white cells counted. In the reported series of observations, no diminution in the glycolytic power of diabetic bloods was found when compared with that of normal subjects when the bloods were kept at 37°. It was also found that at room temperature the glycolytic rates were definitely diminished in both types of blood.—F. S. H.

**The physiological action of insulin** (*Ricerche sul l'azione fisiologica dell' insulina—2a nota*). Serono (G.), Torcello (E.) & Cruto (A.), *Rassegna di clin., terap. [etc.] (Roma)*, 1924, 23, 53-60.

This investigation brings to light new functions of insulin, rec-

ognizing in it a neutralizing action on excess digestive ferments. According to this theory the action of adrenalin is antagonistic to the external secretion of the pancreas and to the digestive ferments in general.—P. M. N.

Total inorganic calcium and phosphorus in the blood of diabetic patients showing a peculiar symptomcomplex. Smith (B.) & West (H. F.), *Tr. Am. Soc. Clin. Investigation*, 1924.

A considerable proportion of patients with diabetes develop a rather definite group of symptoms, which become manifest after they have reached a state of apparently adequate nutrition. These symptoms may reach a point of distressing severity. Prominent in this symptom complex are attacks of weakness (at times approaching collapse), sweating, coldness, nervousness, paresthesias and stiffness of muscles; with the finding of vascular hypotension, rapid pulse, pallor, cold moist skin and poor muscle tone. In occasional instances are seen attacks suggesting mild tetany. This complex occurs most frequently among patients who had become radically undernourished or who previously have had vigorous treatment for some acute diabetic emergency. It occurs among patients who have been treated without insulin, but has been encountered more frequently among those who have had this assistance. True hypoglycemic reactions have been excluded by blood and urine analyses. The finding of a low blood calcium in a few of the patients with more marked symptoms, with a certain amount of relief from calcium feeding, has led to a study of the total inorganic calcium and phosphorus of the blood. As a rule, blood was taken just before the noon meal, which was usually not at the time of acute symptoms. In 25 determinations on 20 patients in good physical condition and not showing these symptoms, total calcium of below 10 mg. per hundred cubic centimeters was found in but two, and these had previously experienced similar symptoms, but were vigorous and doing manual work at the time of examination. The average for the series was 11.45 mg. In 29 determinations on 23 patients showing symptoms similar to the foregoing, only 7 showed calcium of 10 mg. or above. The average calcium of this series was 9.01 mg., with 6.4 mg. as the extreme low finding. Total inorganic phosphorus showed practically the same distribution in the two series, averaging 3.54 mg. and 3.57 mg., respectively. While the evidence is not sufficient to warrant the assumption that calcium disturbance is the sole or primary factor in this symptom complex, the findings seem of definite significance and are offered as a partial study of the condition.—*J. Am. M. Ass.*, 82, 1990.

On the preparation of insulin. Somogyi (M.), Doisy (E. A.) & Shaffer (P. A.), *J. Biol. Chem. (Balt.)*, 1924, 60, 31-57.

A simplified method is described for the preparation of insulin



from beef pancreas. The activity of insulin is probably a property of an individual protein "insulin-protein," the solubility of which is described. The method of extraction from the pancreas and its purification is considered from the point of view of the properties of the "insulin-protein." It has been separated from two other proteins which are also precipitated at their isoelectric points, and which are included in the preparations of insulin, purified by "isoelectric precipitation" as earlier described by the authors. Data are given to indicate the activity of the purified "insulin-protein."

—F. S. H.

The relation between the histological state of segments of transplanted pancreas and glycosuria (*Sui rapporti che passano fra lo stato istologico dei segmenti di pancreas trapiantati e la glicosuria*). Visco (S.), *Arch. di Farmacol. sper. (Roma)*, 1923, 35, 154-160; 167-183.

Histological report of 8 cases of pancreas transplantation, 4 subjects with and 4 without glycosuria. The author thinks that the incretory function of the pancreas should be attributed to the whole organ.—P. M. N.

Present status of diabetic patient as surgical risk. Wilder (R. M.) & Adams (S. F.), *Wisconsin M. J. (Milwaukee)*, 1924, 22, 557-561.

Wilder and Adams stress the fact that the formerly prohibitive mortality which accompanied attempts at surgery on diabetic patients has been materially reduced by skillful surgery, proper anesthesia and the judicious use of medical measures before and after operation. It is unjustifiable to subject a diabetic patient to surgery unless very good surgery and special medical supervision are available. Insulin is a valuable adjunct in the management, but is only one of several important medical measures and will not protect a patient unless it is skillfully administered. An operation may provoke severe acidosis in cases of very mild diabetes, and such cases deserve, therefore, the same scrupulous medical attention as do those of severe diabetes. Three hundred and twenty-seven operations are reported on 251 diabetic patients with four deaths. This gross mortality of 1.2% by operation compares favorably with that of the general surgical list. One hundred and forty-one of the operations were major surgical procedures.

—J. Am. M. Ass., 82, 2084.

The biochemistry of experimental tetany. Creatin of urine and muscle in guanidin and parathyroid tetany with and without calcium treatment (*Zur Frage der Biochemie der experimentelle Tetanie. Harn und Muskelkreatin bei der Guanidin und Parathyreopriven Tetanie ohne und nach Ca-Behandlung*). Palladin (A.) & Griliches (L.), *Biochem. Ztschr. (Berl.)*, 146, 458-466.

It was found that the creatin content of muscle was increased in tetany due to guanidin and to parathyroid deficiency. This increase in muscle creatin gives rise to creatin in the urine, while the creatinine excretion either is increased only slightly or not at all. The experiments show a direct relation between creatin formation in muscle and the creatin and creatinine excretion in the urine. When calcium is given to the guanidine treated rabbits creatin excretion is within normal limits; and the creatin content of the muscles is normal if the symptoms of tetany are aborted. This leads to the conclusion that Paton's theory that the increase of creatin is due to formation in excess amounts from guanidine is wrong.—F. S. H.

**Blood changes and clinical symptoms following oral administration of phosphates.** Salvesen (H.), Hastings (A. B.) & McIntosh (J. F.), *J. Biol. Chem. (Balt.)*, 1924, 60, 311-326.

Experimental results are presented which lead the authors to the conclusion that the clinical symptoms of tetany produced by the oral administration of phosphates to dogs are due to a reduction of the blood calcium. From this it is stated that "the symptoms of parathyroid insufficiency are due to the low blood calcium"

—F. S. H.

**Pineal gland tumor.** Jess (J. H.), *Tr. Chicago Pediat. Soc.*, 1924.

This boy, aged 21 months, was of normal birth, with spontaneous delivery. He was breast-fed for 13 months, and developed normally but learned to walk very slowly. He was first seen when 15 months old, when he was able to stand up and walk around a chair. He was beginning to talk. His mother first noticed that he had pubic hair at about this time, and that the genitalia were larger than normal. His voice has always been very coarse, and all measurements are in excess of the average for his age. His head is larger than normal and the features are those of a much older child. Pubic hair is present. The right testicle is about the size of a walnut, the left about two-thirds that size. There is no evidence of a tumor mass, although one is much firmer than the other. Roentgenologic examination of the head and sella turcica gave negative findings. There are no focal findings, such as might be due to intracranial pressure. There is no nystagmus, no paralysis of the eye muscles. The sight is good and the fundi are normal. There is no evidence of involvement of the suprarenals, and while the genitalis are much more advanced in their development than is normal for his age, the size and shape of the skull and retarded mental development have led the author to believe that there was some intracranial pathologic change. The Wassermann and tuberculin tests are negative. Clinical reports of similar cases show that in most instances homosexual changes in the male have followed tumors of the pineal gland, while heterosexual changes have

been secondary to involvement of the suprarenalis.—Am. J. Dis. Child, 28, 123.

**Status thymicolymphaticus.** Delgado (H.), Rev. de psiquiat. y discip. conex., 1924, 5, 40-55.

The author discusses the different factors in this condition, especially its etiology, pathology and diagnosis. The clinical symptoms are described, particularly those of pluriglandular origin and the vago-sympathetic disturbances. Among the syndromes due to status thymicolymphaticus Delgado points out its close relation to epilepsy and reports some protocols to this effect. He reports, too, a case of mors thymica and discusses some of the theories attempting to explain it.—A. M. Q.

**Physiological and therapeutic importance of the thymus** (*L'importanza fisiologica e terapeutica della ghiandola timo*). Gagliardi (A.), *Terapia* (Milano), 1924, 14, 47-53.

A report of observations on the physiological action of the thymus, with particular consideration of its relation to tuberculosis.  
—P. M. N.

**The diagnosis and treatment of enlarged thymus.** Grier (G. W.), *Am. J. Roentgenol.* (N. Y.), 1924, 11, 141-144.

One should be on the alert for enlarged thymus in young infants, especially in those of premature birth. Heavy breathing, a crowing inspiration and later on a failure to thrive should direct suspicion to this condition. It should be remembered that the thymus enlarges greatly when the baby cries. Radium treatment is practically a specific. The dosage required to produce a favorable result is not large and the author says that the thymus can be sufficiently reduced without producing an erythema of the skin. There are many minor differences in technique which do not materially alter the final result, but if one follows a prescribed technique he should adhere to it strictly. The main factors governing dosage are the quantity of radium used, its distribution, whether in one or several capsules, the distance from the skin and the number of areas treated. "One hundred milligrams of radium in one capsule and moved about over different areas has a different effect from the same quantity divided into four capsules of 25 mg. each and scattered about over one area, even if the same distance from the skin and the same number of milligram hours are used. It should be remembered that where adjoining areas are exposed, such area receives a part of the dose when the adjacent area is exposed. In ordinary sized area of about one by two inches this extra dosage amounts to about one-quarter of the dose applied to each area, so that if other adjoining areas are treated, each area receives exactly twice the dose directly applied to it. The technique which I have

used satisfactorily for some time is to place four tubes of radium, each containing 25 mg., in a wooden block with holes bored in it one inch apart to contain the capsules. The filter used is one millimeter of brass. The block is left in position for ten hours with the radium at a distance of three-fourths of an inch from the skin. This dose does not produce any erythema, and usually one treatment is all that is necessary, although occasionally it has to be repeated. It is an entirely safe dose and can be increased to twelve or fourteen hours if desired, although I have not considered it necessary."—J. Radiol., 4, 181.

Relation between the thymus and the genital organs (Beitrag zur Physiologie der Thymus. Über die Beziehungen zwischen Thymus und Generationsorganen). Knipping (H. W.) & Rieder (W.), Ztschr. f. d. ges. exper. Med. (Berl.), 1924, 39, 378-384.

Should guinea pigs after coming to puberty be divided, some being cut off from sexual intercourse and others induced to vigorous sexual activity, the average weight of the thymus of the animals kept separate is about 27% higher than that of the animals to which sexual activity has been allowed. Histologically the point at issue is that the abstaining animals show a simple persistence without sign of general or specific hyperplasia, while the glands of the other animals show physiological involution.—Physiol. Abst., 9, 183.

The diagnosis of enlarged thymus by the x-ray and treatment by x-ray or radium. Pfahler (G. E.), Arch. Pediat. (N. Y.), 1924, 41, 39-46.

The thymus can be enlarged without producing symptoms and, on the other hand, thymic symptoms may develop even when no enlargement of the thymus is shown by the x-ray. For by the x-ray we can show only lateral enlargement and yet it is the anterior-posterior pressure which causes the symptoms. The therapeutic test is more reliable than the x-ray diagnosis, as in nearly all cases the symptoms are relieved by radiation. Lymphadenitis of the upper mediastinum in some instances resembles very closely enlarged thymus of slight degree. The shadow in these mild cases is not characteristic and therefore it is difficult to make a positive diagnosis. Both thymic enlargement and lymphadenitis yield to radiation. Heavy breathing, wheezing or crowing respiration, cyanosis or an abnormal cry should direct attention to the thymus. The thymus enlarges when the baby cries. X-ray or radium treatment is a specific, but must be applied with caution, accuracy and skill. Radium is probably preferable and safer and when one considers that only one application is necessary it is probably as cheap.

—M. B. G.

The influence of thymus extracts on capacity for work and fatigability of mammalian muscle (Ueber den Einfluss von Thymusextrak-

ten auf die Leistungsfähigkeit und Ermüdbarkeit des Säugetiermuskels). Thurner (K.), Arch. f. d. ges. Physiol. (Berl.), 1924, 202, 444-467.

Intravenous injection of thymus extracts produces a distinct increase in the work capacity of fatigued striped mammalian muscle. The alcohol extract is especially active; its active principle is thermostable. Alcohol extracts of other organs do not produce the effect. Choline is not the active principle. The action on unfatigued muscle is uncertain, and in any case slight.—A. T. C.

Substances with specific action prepared from single organs IX. (Studien über die von einzelnen Organen hervorgebrachten Substanzen mit spezifischer Wirkung IX.). Abderhalden (E.) & Schiffmann (Olga), Arch. f. d. ges. Physiol. (Berl.), 1923, 198, 128-144.

It is not possible to influence the metamorphosis of tadpoles either by feeding frogs with thyroid before spawning, by treatment of unfertilized eggs and sperm with active substances, or similar treatment of fertilized eggs. Tadpoles show typical thyroid action after feeding any of 3, 5-l-diiodotyrosine, 3, 5-d-l-diiodotyrosine, iodized silk peptone, thyroglobulin, or iodoalbumen D, iodoserum-albumen A and D (Blum and Strauss' preparations). Tyrosine plus potassium iodide, dibromotyrosine, phenylalanine, p-iodophenylalanine, and silk peptone are all without action. Tadpoles which show the typical action of thyroid have a lessened liver glycogen content.

—A. T. C.

Gas metabolism and metamorphosis of amphibian larvae after feeding thyroid or iodine containing substances (Gaswechsel und Metamorphose von Amphibienlarven nach Verfütterung von Schilddrüse oder von jodhaltigen Substanzen). Abelin (I.) & Scheinfinkel (N.), Arch. f. d. ges. Physiol. (Berl.), 1923, 198, 151-163.

Thyroid feeding to larvae of *Rana esculenta* and of Axolotl, leads to accelerated metamorphosis, with decreased carbon dioxide production (50 to 70% of normal) during the metamorphosis period. Di-iodotyrosine and di-iodotyramine produce similar results. Initially, in all cases, there is a slight rise in carbon dioxide output, and it is suggested that this increased gas metabolism may be the actual stimulus leading to the metamorphosis. Iodine does not accelerate metamorphosis in axolotls.—A. T. C.

Thyroid treatment of early stages of arthritis (La cura tiroidea nelle forme iniziali di artrite). Baccarani (U.), Rassegna di clin., terap. [etc.] (Roma), 1924, 23, 1-5.

Obese, plethoric and gouty patients with painful manifestations were treated with "tiroidasi Serono." No results were seen for

about two months, after which improvement set in. A year of such treatment was found to bring about good results.—P. M. N

The thyroid in its relation to the nervous and mental systems. Ball (C. R.), Minnesota Med. (St. Paul), 1922, 5, 423-426.

This is a brief review of current opinions regarding the nature of thyroid malfunction. The thyroid problem is not one which concerns the thyroid alone, but consists of many morbid processes due to generalized maladjustment. The hyperthyroid type is especially significant of a stigma of constitutional inadequacy.—I. B.

Mitochondria content of the thyroid as an index of the activity of the gland. Bolt (W.), J. Lab. & Clin. M. (St. Louis), 1924, 9, 630-633.

In 1916 Goetsch reported that the mitochondria of the thyroid are markedly increased in toxic adenomata. Bolt has extended the work by a study of various cases of exophthalmic goiter and of toxic adenomata. In these, Goetsch's findings were confirmed. Of particular interest were Bolt's findings in 6 cases of colloid goiter, in 5 of which toxic symptoms had developed. In one non-toxic case the mitochondria were normal. In 4 of the 5 toxic cases the mitochondria were augmented. In one of these no other morphologic evidence of toxic activity of the thyroid could be found.—R. G. H.

Influence of iodine on the thyroid (Bemerkungen zur Iodwirkungen auf der Schilddrüse). Breitner (B.), Wien. klin. Wchnschr., 1923, 36, 603-605.

The thyroid regulates the iodine metabolism of the organism. Breitner considers the colloid as the product prepared by and kept in the thyroid and thinks that when the body needs iodine colloid flows into the blood. Iodine, he states, influences different goiters differently because goiters contain different amounts of colloid. The author believes that in Graves' disease the iodine-protein compound of the thyroid is of inferior quality. Increased activity of the thyroid may be helpful. Small doses of iodine may have a good influence on the iodine-protein compound.—J. K.

Tendon reflexes in myxedema: a valuable aid in diagnosis. Chaney (W. C.), J. Am. M. Ass. (Chicago), 1924, 82, 2013-2016.

In cases of myxedema, the tendon reflexes produce such slow movement of the parts affected that the quality can be recognized without the aid of mechanical devices and is regarded by Chaney as being a valuable sign in the diagnosis of the disease. In cases of myxedema, a greater stimulation is necessary to elicit a tendon reflex than in a normal person. The period or time interval of a tendon reflex of any person under the same conditions remains the same, and seems independent of the amount of stimulation applied.

In all conditions associated with a low basal metabolic rate studied to date, with the exception of myxedema, the tendon reflexes seem to correspond in every way with those of a normal person. When a patient with myxedema is treated and brought back to normal so that he loses the usual characteristics of this disease, his tendon reflexes also seem to return to normal, and the approach of the reflexes to normal seems to keep pace with the basal metabolic rate.

—Courtesy A. M. A.

**Physiology of the thyroid.** Charvát (J.), *Casop. lék. česk.* (Prague), 1924, 63, 801-805.

Charvát injected intravenously 1 cc. of a 10% solution of sodium iodid per 10 kg. of body weight. The iodine disappeared from the blood faster in hyperthyroidism than in the healthy controls. The blood sugar was not changed or only slightly decreased in normal subjects, while it was increased in hyperthyroidism. It decreased in one patient with exophthalmic goiter, who was, however, increasing in weight before the test was applied.

—J. Am. M. Ass., 83, 78.

**Adolescent hyperthyroidism.** Cole (W.), *Arch. Pediat.* (N. Y.), 1923, 40, 703-707.

A boy 12 years of age, complaining of nervousness, dyspnea, attacks of flushing and loss of weight, improved under the treatment. The boy's mother had a goiter. The treatment consisted of complete rest in bed, low nitrogen diet, light general massage, quinine hydrombromide and sodium bromide.—M. B. G.

**The biological test of thyroid substances in blood** (Ueber den biologischen Nachweis von Schilddrüsenstoffen im Blut). Csillag (Elisabeth), *Arch. f. d. ges. Physiol.* (Berl.), 1924, 202, 588-595.

Eiger's result, that in very great dilution thyroid extracts still increase the action of adrenin on the Læwen-Trendelenburg preparation, is confirmed, but the effect cannot be used as a test for the detection of thyroid substances in blood, since blood plasma of normal and of thyroidectomized rabbits, and of normal man and subjects of Graves' disease always itself increases the adrenin action.—A. T. C.

**Heart, pulse and blood pressure in exophthalmic goiter** (Cuore, polso e pressione nel morbo di Flajani-Basedow). Falconcini (R.), *Riforma med.* (Napoli), 1922, 38, 465.

A report of 12 cases. There was tachycardia and dilatation of the heart (although not always accentuated in its transverse diameter), arrhythmia and extrasystole. The blood pressure was decidedly increased in all cases. The pulse was almost normal except for catacrotism and polygeminism due to extrasystoles.—G. V.

The growth of hair and compensatory hyperplasia of the thyroid after operative removal of incertory glands (Beiträge zur Physiologie der Drüsen. L. Asher. Experimentelle Untersuchungen über den Einfluss der Drüsen mit innerer Sekretion auf die Wachstumsvorgänge, zugleich Beiträge zum Konstitutionsproblem. III.) Furuya (K.), Biochem. Ztschr. (Berl.), 1924, 147, 425-432.

A normal rabbit regenerates hair within 4 weeks after an experimentally produced defect. When the ovaries are removed this recovery is much less, and when the thyroid is taken out practically no regeneration occurs. The authors believe that they have shown a sex-specific relation between thyroid and gonads in rats and dogs, from the fact that they observed a much greater compensatory hypertrophy or hyperplasia of the thyroid residue in females than in males when one-half was removed. The removal of the testes seemed to exert a retarding effect on residual thyroid tissue enlargement. The number of experiments was very few.—F. S. H.

The rôle of the thyroid in coal-gas and adrenin-glycosuria and hyperglycemia (Untersuchungen über die Rolle der Schilddrüse beim Zustandekommen der Leuchtgas und Adrenalinglykosurie bzw. Hyperglykämie). Geiger (E.), Arch. f. d. ges. Physiol. (Berl.), 1924, 202, 629-641.

Coal-gas poisoning produces no glycosuria in thyroidectomized dogs; the hyperglycemic curve is the same as that for normal dogs. The absence of glycosuria must therefore be referred to changes of kidney function. Thyroidectomy does not affect the hyperglycemia following adrenin injection.—A. T. C.

Tuberculosis and the endocrine glands. I. The thyroid (Tubercolosi e ghiandole endocrine—Nota 1a: Tiroide). Gelmi (E.), Gior. di clin. med. (Parma), 1924, 5, 213-221.

Slight hyperthyroidism acts favorably on tuberculosis, but severe hyperthyroidism is harmful. The role of the thyroid in tuberculosis is not yet clearly shown.—P. M. N.

The psycho-electro-tacho-gram (thymogram) and exophthalmic goiter (morbus-basedowi). A contribution to the experimental psychopathology of exophthalmic goiter. Godefroy (J. C. L.), Psychiat. en Neurol. Bl., 1922, No. 3/4, 133-173; abst., Ber. ü. d. ges. Physiol. (Berl.), 1923, 18, 122.

By connecting a transformer of alternating current the ordinary abducible current of the cutaneous surface (psychogalvanic reflex phenomenon) is transformed into the form of a tachogram. The deviation from the balancing position corresponds to the current variation, thus the deflection forms a plane between the usual curve and that of the tachogram and this corresponds to the amount



of electricity developed by way of a psychogalvanic reaction. The advantage of this transformation lies especially in the fact that it does not approach the height so much as the form of a psychogalvanic current curve. This form stands out rather sharply in a tachogram. The increased affect lability of Graves' disease can be demonstrated in many cases. The Mollisch rotary coil galvanometer was used.—R. G. H.

The effect of thyroparathyroidectomy and parathyroidectomy at 100 days of age on the growth of the brain and spinal cord of male and female albino rats. Hammett (F. S.), *J. Comp. Neurol.* (Phila.), 1923, 35, 313-335.

The brain is more dependent on thyroid function for its proper growth and differentiation than is the cord. The growth of the central nervous system is more resistant to the harmful effects of the toxemia induced by parathyroid loss than is that of the body as a whole. The causes of the greater retardation of brain growth, as compared with the growth of the cord, lie in the lesser inherent growth ability of this organ, the high protein-low lipid composition of the brain as compared with the high lipid-low protein composition of the cord and the apparent relatively less dependence of lipid formation and deposition on the anabolic function of the thyroid than is found in cytoplasmically active material. The change induced in the differentiation of brain and cord from the normal, after thyroid loss, is indicative that the growth of the brain is qualitatively as well as quantitatively altered by this procedure. The differences in degree and nature of the changes in differentiation of the brain and cord in conditions of chronic parathyroid deficiency are not sufficient to warrant any definite conclusion as to their significance.—Abst., Wistar Inst.

The growth of the heart, lungs, liver, kidneys, spleen, submaxillary glands and eyeballs in male and female albino rats thyroparathyroidectomized and parathyroidectomized when 100 days of age. Hammett (F. S.), *Am. J. Anat.* (Phila.), 1923, 32, 75-94.

The lack of thyroid (thypar) secretion causes an absolute inhibition and retrogression of the growth of the heart, lungs, liver, kidneys and spleen of albino rats of both sexes. The growth of the liver in the females is only retarded. When parathyroid secretion is lacking, simple retardation is shown by the heart, lungs, liver and kidneys. Spleen growth is apparently accelerated. Submaxillary growth is inhibited by thyroparathyroidectomy, while parathyroidectomy is followed by submaxillary enlargement. The growth of the eyeball seems to be quite resistant to thyroid and parathyroid deficiency. The significance of these observations is discussed.

—Abst., Wistar Inst.

The effect of thyroparathyroidectomy and parathyroidectomy at 100 days of age on the Ca, Mg and P content of the ash of the humerus and femur of male and female albino rats. Hammett (F. S.), J. Biol. Chem. (Balt.), 1923, 57, 285-303.

There is no definitely detectable differentiation in the chemical composition of the humerus and femur of normal rats during the age period from 100 to 150 days. When the thyroid apparatus is removed the ossification ability is decreased. In both bones of both sexes there is a slight shift in the nature of the ash deposited. The direction of this shift is toward a higher percentage of magnesium and phosphorus than the normal. This is believed to be an effect of the parathyroid deficiency since it is shown to a much more marked degree in the parathyroidectomized rats. No change in the percentage of calcium was caused by thyroparathyroidectomy or parathyroidectomy in the male rats. It is therefore clear that although the calcium-retaining ability of the organism is reduced by lack of function of both the thyroid and parathyroid glands the process of calcification is undisturbed. This is evidence that the formation of a bone ash of normal calcium content is not directly related to thyroid or parathyroid function. The ash of both bones of the parathyroidectomized females had a lower percentage of calcium than the normal. The same was true, but to a lesser degree, of the ash of the bones of the thyroparathyroidectomized females. It is therefore probable that the lower calcium found here is to be associated with parathyroid rather than thyroid deficiency. This low calcium in the ash of the bones in the female is possibly attributable to a combination of ovarian and parathyroid deficiency.

—F. S. H.

Post-partum hyperthyroidism (un cas d'hyperthyroïdisme des suites de couches). Laffont, Bull. Soc. d'obst. et de gynéc. (Par.), 1923, 12, 301-302.

Placenta preparation, fed to a primipara to stimulate milk secretion was followed by symptoms of hyperthyroidism which subsided on discontinuing of the medication.—F. S. H.

A consideration of the diseases of the thyroid gland. Mastin (E. V.), South. M. J. (Birmingham), 1924, 17, 345-349.

This is a brief recapitulation without new material.—J. C. D.

The relation of the function of the thyroid to the amount of nitrogen contained in viscera. Ryu (M.), Nihon Naikagakukai Zasshi (Tokyo), 1923, 2, 833-868.

The author estimated the quantity of rest nitrogen, urea, ammonia, amino-acid, creatinin and creatin in the liver, kidney, heart, muscle, spleen, and brain of normal, thyroidectomized and thyroid-fed rabbits. The amount of rest nitrogen decreased in the liver, kidney, heart, muscle and brain after removal of the thyroid, while

that of the spleen seemed to be slightly increased. An increase was found in all viscera, except the brain, in the animals fed with thyroid. Urea decreased in the liver, kidney, muscle and brain of the animals with thyroid removed, and increased in several viscera of those fed with thyroid. A slight increase in the amino-acid content of the liver, kidney, heart and muscle was found in both the thyroidectomized and thyroid-fed animals. Ammonia increased in the kidney, heart and spleen, but decreased in the muscle and brain after removal of the thyroid, while it increased in all the viscera on feeding with thyroid. Creatinin increased slightly in the kidney, but it showed no marked change in liver, heart and muscle after removal of the thyroid. A slight increase was found in the kidney, but a decrease in the muscle on feeding thyroid; there was marked change in other viscera. The change in the amount of creatin was very interesting. It decreased in animals with the thyroid removed, but this decrease was much more evident in those fed with thyroid.—K. H.

**Experiences in the campaign against goiter among young girls above school age by means of iodine tablets** (*Erfahrungen über Kropfbekämpfung mittels jodhaltigen Tabletten bei älteren, schulentlassenen Mädchen*). Silberschmidt (W.), Schweiz. med. Wchnschr. (Basel), 1923, 53, 637-639; Bull. mens. office internat. d'hyg. publique, 1923, 15, 1376.

The author describes the use of chocolate tablets containing 0.5 mg. iodine at the rate of one tablet per week for two years. The results were good with girls from 15 to 21 years of age, but not so good as those with younger children. Silberschmidt advises against too great expectations from the use of iodized table salt, although its use is free from danger. Less satisfactory results are to be expected in relieving goiter among adults than among children.

—Chem. Abst., 18, 1338.

**Bile salt metabolism. II. Proteose and x-ray intoxication. Thyroid and thyroxin.** Smyth (F. S.) & Whipple (G. H.), J. Biol. Chem. (Balt.), 1924, 59, 637-646.

Thyroid extract and thyroxin given to dogs in sufficient dosages to cause an increase in the urinary nitrogen do not modify appreciably the bile salt output under the conditions of the experiments.

—F. S. H.

**Results of iodine administration in exophthalmic goiter.** Starr (P.) & Means (J. H.), Tr. Am. Soc. Clin. Investigation, 1924.

Patients with exophthalmic goiter have been given by mouth 15 drops of compound solution of iodine daily. Determinations of their basal metabolic rate, pulse and weight were made daily, or at intervals of a few days, for weeks and months. In many cases a

great drop in metabolic rate began soon after iodine was started. Cases with metabolic rates of plus 50 or 60 fell within a few days to plus 10 or 20; others fell to zero or below. This amounted to complete remission of the disease, and is similar to that following subtotal thyroidectomy; the pulse became slow; appetite became normal; nervousness and tremor diminished, and weight increased. We feel that iodine produced this crisis since with a remission in treatment prompt recrudescence of the original disease occurred. Most of our patients were operated on or received roentgen-ray treatment after this drop in metabolic rate, but some that were given iodine for several months had, nevertheless, a gradual recurrence. The primary drop in the out-patients required about a month, in contrast to the immediate drop in the patients at rest in the hospital. After another month the basal metabolic rate increased again, reaching its original toxic level in two more months. The patients were then successfully operated on. Continuance of the iodine probably did not cause the return of the disease, since in those cases in which it was stopped during the recurrence a still greater rise occurred. Certain patients receiving compound solution of iodine and roentgen-ray simultaneously were at normal limits at the end of five months. Another group of subjects, including several with exophthalmic goiter and with toxic adenoma, were apparently unaffected by the administration of iodine. We conclude that large doses of compound solution of iodine by mouth produce abrupt remission in many cases of exophthalmic goiter. The rate of drop is as rapid in these cases as that following subtotal thyroidectomy. Iodine is the effective agent, as its withdrawal is followed by abrupt recurrence of the disease. Iodine alone, as now given, has not been shown to be sufficient to suppress the disease permanently. Iodine and roentgen-ray treatment have been successfully combined in the treatment of some cases. In some cases iodine has no apparent effect.—J. Am. M. Ass., 82, 1989.

**The cardiac disturbances associated with diseases of the thyroid gland.** Wilson (F. N.), J. Am. M. Ass. (Chicago), 1924, 82, 1754-1756.

Most of the cardiac abnormalities produced by thyroid disease occur in those toxic states in which there is an elevation of the basal metabolic rate. So far as the disturbances of the cardiovascular system are concerned, there is little difference between typical exophthalmic goiter and so-called "adenoma with hyperthyroidism." In discussing the cardiac aspects of these conditions, Wilson distinguishes between primary and secondary disturbances of the heart. Under the former heading he includes those cardiac symptoms and signs which occur invariably, or almost invariably, in severe cases of thyrotoxicosis, and which may be considered, therefore, cardinal manifestations of thyroid intoxication. Under

the second heading, on the other hand, he includes those cardiac abnormalities which, because of their relative infrequency, or because their frequency and intensity do not vary directly with the intensity of the other symptoms of the primary disease, may properly be looked on as complications. Of the primary disturbances of the heart, sinus tachycardia and the evidences of overactivity of the heart associated with it are the most common. Of the cardiac complications of thyrotoxicosis, enlargement of the heart is one of the most important. Clinical evidence of myocardial changes in toxic goiter is by no means rare. Death resulting purely from the cardiac complications of toxic goiter is relatively uncommon. It is true that, in so-called postoperative thyroid shock, auricular fibrillation, with extreme ventricular tachycardia and indications of cardiovascular collapse, are seen; but necropsies in such cases usually show severe degenerative changes in the liver and other parenchymatous organs, indicating death from profound toxemia. It is probable that death results in such instances from overwhelming intoxication, in which the heart suffers along with the other vital organs. Milder grades of cardiac weakness are not infrequent, and should be treated exactly as under other circumstances, by rest; morphin when necessary to relieve dyspnea or insure complete rest and sleep; digitalis in amounts sufficient to produce its characteristic effects, and a proper diet. The diet should be designed to meet the caloric requirements, or, perhaps, for the first few days, to fall somewhat below them; it should contain only sufficient protein to prevent a negative nitrogen balance, and should be poor in salt. As to whether adenomatous goiter without hyperthyroidism may damage the heart, it is difficult to form an opinion. Nevertheless, it is clear that a persistent enlargement of the thyroid gland, even though it be regarded as non-toxic at the time of the examination, is at least a potential menace to the myocardium.

—Courtesy A. M. A.

**Hydroelectrotherapy in exophthalmic goiter** (*L'idroelettoterapia nel gozzo esoftalmico*). Vinaj (A.), *Riv. di idrol. climatol. e terap. fisiol.* (Milano), 1924, 35, 106-110.

This treatment is said to be useful in the early stages of the disorder, whether used in connection with opotherapy or not.

—P. M. N.

# Endocrinology

## *The Bulletin of the Association for the Study of Internal Secretions*

November, 1924

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### RELATION BETWEEN CLINICAL AND EXPERIMENTAL ENDOCRINOLOGY\*

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Our association has now enjoyed seven years of not only continuous but increasingly important existence. From our first annual meeting held in New York City in 1917, at which a comparatively few charter members told one another in glowing terms what they expected to do in order to advance to a dignified position the infant member of the medical sciences, to the present meeting in Chicago, our gatherings have gained in importance. We now can point to actual accomplishments in this very limited time. The papers presented here today give evidence of distinct advance. Our membership contains many of the most prominent physicians not only of our country but also of Europe and South America. Nevertheless it was but a few years ago that a distinguished though discouraged gentleman told us that we were sailing uncharted seas, that we knew not whither we were bound, and that perforce we should stop until the depths were sounded and beacons erected—and by implication, the new lands mapped.

He discoursed about the foolish things that had been said and became even somewhat self-accusatory in attaching blame to

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\*Presidential Address delivered before the Association for the Study of Internal Secretions, Eighth Annual Session, Chicago, June 9, 1924.

himself for having given rise to speculations regarding the influence of the pituitary on mentality. His address left his hearers in a quandary and in depression. Was all this work, all their observations, all their conclusions, faulty? Was their work worth while? Ought they not stop and wait? Then, after mature consideration, came the question, self asked: wait for whom? for what? It was as though the Italian navigators of the fifteenth century, laughing as they did at the stories of those that had sailed beyond the Pillars of Hercules and, returning, had given extravagant accounts of their adventures, had also stopped and waited. They had no chart—or, worse still, those they had were in large measure imaginative. A few like Behaim had the temerity to indicate the earth as a globe, and were in dire stress for their lives and liberties thereat. But in all the extravagant stories, and even in the maps, there was more than a grain of truth hidden in the mass of description. America would still have remained undiscovered had there not been a Columbus, who, without any but the most primitive, and those incorrect, charts—in spite of the laughter, the unbelief and the oppression—sailed west.

And in answer to the question, Whither are we bound? we need only answer: What matter, so long as fallow fields and virgin woods mark our way? Columbus reached America, though bound for India!

Indeed, hardly was the ink of his address dry than the world was startled, and of course the medical part of the world cynically so, by the announcement from Toronto of Banting's great discovery of what has come to be called insulin, which I venture to say will prove to be one of the outstanding historical landmarks in medicine. The medical pessimists ran to cover, the therapeutic nihilists still think there must be some mistake. It is this spirit of—not conservatism, as by some it is called, for true conservatism is not opposed to advance—but negativism, or nihilism, or even fetichism, that keeps medical progress tied to old masters, old thoughts and methods of thinking, with thongs as strong as superstition. As recently, comparatively, as one hundred years ago—to be exact, 1819—in one of the Croonian lectures, John Cooke of London, in a discourse relating to certain forms of nervous diseases, cites page after page authoritatively

from Galen, who lived fifteen hundred years earlier! Is this conservatism? Then let us reintroduce the lictors and the Praetorian Guard. And I am not entirely certain that these delectable institutions are not being brought out of their tombs to re-enter service. To introduce a new term—this is “stationaryism,” or “akinesia,” and has no place certainly in a world of flying machine and radio-activity.

Now please let me be understood. It is not my thought that advance in our subject must be necessarily swift or that it must be sensational. Neither that it must be continuous. In practically all fields of human endeavor, progress is the difference in the ground covered between advance and retreat. That is to say, much that has been offered as new cannot withstand the test of long continued trial and so must be retracted or rescinded, leaving only a modicum to represent the real net value of the forward movement. And this give and take, this backing and filling, is a continuous tidal movement; now we are on the flood, now in the ebb; and he who predicates the future while in either phase of motion, carried away by the environmental trend, without giving due consideration and weight to its complement, must go astray and lead his followers into extremes of pessimism or optimism. And so when we regard all the tremendous mass of material that in the study of the internal secretions has accumulated in the past decade, of course we must also consider the onset of the ebb, and the large part of this will by it be carried off. But there will remain much that is good and true and helpful. From the very nature of things, advance in this subject must be in all realms that deal with life in all its forms, and so we have contributions to the subject from all kinds and types of laboratories and clinics; the biologists, the geneticists, the morphologists, the physiologists, the biological chemists on the one hand; and the various clinicians on the other—the gynecologist, the surgeon, the internist, the pediatricist, the neurologist. Indeed, no specialty is so poor that it cannot boast some endocrine trouble-maker. Now you can readily see that in each of these fields, both laboratory and clinic, disagreement as to results must follow, and this disagreement, based upon differences in approach and method, at times with and more often without the possibility of proper control, has given rise unfortunately to as



many camps as there are specialties; but the two real antagonistic groups may be represented by the laboratory workers and the clinicians, and the reason for the difference between these two great groups is not far to seek. Let me try to give a picture of each of these camps viewed from the other. The material put out by the clinician, says the physiologist, is without proper observation, without proper control, not enough proper evidence from which to draw conclusions, and so worthless from a scientific point of view. Says the clinician: Here is our friend the physiologist, who wants us to wait and wait and wait until he gives us something definite or positive or worth while to work with, and when he finally publishes something it is like a court decision—one doesn't know whether it is yes or no until it is read a dozen times, and then it concerns itself only with some subordinate or accessory fact. If we wait to help our patients until the physiologist tells us what to do, another glacial era will be upon us. And worst of all, some other physiologist will then disagree with our friend. The clinician, says the physiologist, hasn't enough selected material and no controls and cannot prove his statements, and hence is not fitted to tell us the whys and wherefores of human difficulties. The physiologist, sniffs the clinician, gets his facts from laboratory guinea pigs and rats, which are not immediately applicable to free humans, if indeed they are, in an unlimited sense, at all. Some investigators, beginning with Vesalius, believe this. They will cite, for instance, the diametrically opposite effect of morphine on the pupil of the eye in the cat as compared with man. Furthermore, it is extremely doubtful whether blood sugar determinations in the carnivora—cats and dogs—are applicable to man. The clinician cites five hundred consecutive cases of a disease entity which is thrust upon him, such as typhoid or encephalitis, and groups them into classes of resemblances and differences and tries to get a percentage solution in the symptomatology or in the treatment. The physiologist takes a definite problem, arranges his specimens into "operatives" and "controls," and endeavors to get a definite answer to his query through his protocols. Both are right and both are wrong. While a percentage basis of diag-

nosis or therapy may hold good in one series or in one epidemic, epidemics differ in their incidence and manifestations, and what were thought valid rules of procedure at one time give way to newly formulated ones at another. Nothing is fixed or permanent. The physiologist, on the other hand, determines the truth or falsity of some very limited proposition, and this, analogous to a mathematical theorem, remains the truth and unchangeable for all time. But, differing from mathematics, he does not begin with a fixed, perfectly circumscribed and defined material, but with a living, changing individual. And hence when he reduces his observations and his precise instrument readings to the fourth or sixth decimal point, while it looks quite precise and mathematical and at times even awesome, yet after all it is only a matter of recording his own observations, and every error in them is likewise carried to four or six decimal places. An excellent illustration, and one that is always regarded as the acme of the possibilities of a scientific laboratory, is that famous discovery of the planet Neptune, by Leverrier. In his laboratory, Leverrier determined from the observed perturbations in the movements of the known planets that there must be one mass as yet unaccounted for that produced these perturbations, and that its orbit ought to occupy a certain place in the heavens. And looking for the mass in this theoretical orbit at the appropriate time and place, Adams and others found it—the planet Neptune. So far, so good; but it turned out that not only were his observations faulty but his mathematical astronomy incorrectly applied, so that Professor Peirce of Harvard stated that Leverrier's calculations would have been as well applicable to other orbits, and that it was only by a lucky chance that the new planet was discovered! The greatest scientific laboratory discovery thus was shown to be on a par with the so-called accidental discoveries in medicine. The shrewd observations of Jenner were on a higher level, and the abysmally ignorant South American savages that gave us quinine didn't even know its formula.

The main differences then are: not that one class of medical men are better observers or better logicians or better mathematicians than the others; but that in the one case they observe the

things that a continuous stream of life places before them, though they cannot choose their material; while in the other they themselves pick the creatures they wish to observe, and arrange the details so that the smallest possible differences are created between normals and selected ones, and these differences and their implications are studied. The physiologist can cut out all the disturbing and interfering factors in his experimental studies, almost at will, while the clinician must allow for them in his calculations and observations; hence the qualifications necessarily included in the latter's conclusions. The physiologist, cutting out all disturbing factors, deals with "artificialized" life.

One of the best illustrations of the differences in method is that furnished by the substance adrenalin. It is now nearly three decades since Oliver and Schäfer noted that adrenal extracts cause augmentation of the heart beat. On the basis of such observations adrenalin has come into wide use as a cardiac stimulant. But how does adrenalin strengthen the heart beat? Here is the crux of the situation: should the clinician have waited, in spite of his observation that adrenalin in some way does stimulate the heart's action, until the ground on which he stood had been perfectly charted and mapped, and the reason for and path of the stimulant had been furnished him, before he made use of his empirical knowledge? The physiologists, by implication, say yes: for they tell us to wait for charts, soundings and beacons. If the Greeks or the Egyptians had waited to use ligatures on arteries in their operative procedures, or compression to still the bleeding from wounds on the battlefield, until Harvey had proved to them that the blood circulated, King Tut-ankh-amen might have had no more followers than a desert sheik. For that they did this especially in their frequent operations of castration, no less an authority than Celsus tells us. It was even customary among them to tie arteries in two places, cutting the vessel between them.

On the other hand, the many published statements made by clinicians upon insufficient evidence and faulty observation, and the attempted explanations to account for the most complex and

intricately interwoven phenomena, have led their followers into many a difficult situation from which ignominious retreat was the only solution.

The clinician's function and that of the physiologist should be mutual and cooperative. If, in the expedition against disease, the clinician did not put up a hastily constructed shack against the rigors of the elements, the entire party might be snowed under, or frozen to death, or washed away. True, the shelter is a bit leaky and trembles somewhat in the gale and must be constantly patched and supported; but at any rate it is a shelter. Later on, with a firm foundation and carefully adjusted walls, there is reared by the physiologist of the group, very slowly but surely, a firmer structure which may defy the storm permanently. The scout clinician may then safely, from his permanent station, again emerge for new reconnoitering and exploration purposes. The same processes of temporary shelter and permanent home are again established, and so we go on. One laughs at the other's slowness, the other grins at the first's temerity, and both mutually exchange language. But with all these incidentals the whole party moves along, grumbling and fault-finding as all good soldiers do, but gradually and surely enveloping and overcoming the enemy. But let there be no separation, no division, no rebellion; for then we must all become disorganized and our advance checked. And not only that, but our differences, distorted and magnified by the host of unknowing whom we try to save from themselves and the consequences of their own folly, seem to establish a basis for the adverse criticism and contumely so constantly heaped upon us. Let there be in the future, not a divided camp with mutually cynical component groups of physiologists and clinicians, but a coordinate, cooperative corps, of course with its differences and its competitions, but all engaged, through an exchange of views and experiences of laboratory research and clinical investigation, in the mutual assistance so necessary to the solution of the problems involved in medical sciences.

To fall short in this work is to stamp ourselves simply inadequate; but if the inadequacy is due to our own internecine strife, then our deficiency is a moral one as well.

Let me, whom you have honored by election to the presidency of our organization, exhort you, physiologists and clinicians, to cast aside your cynicism, to work in good humor and harmony toward the common goal of medicine—the freedom of mankind from the ills and incapacities of disease.

# THE USE OF IODIN IN EXOPHTHALMIC GOITER \*

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ROCHESTER, MINNESOTA

Iodin has been the active agent in most of the remedies recommended for goiter since the twelfth century, when Roger, of the University of Salerno, discovered the value of the ashes of sponge and seaweed in this connection. Coindet in 1820, however, was the first to recognize the fact that the beneficial agent in the various concoctions administered for goiter was iodine. In a series of papers beginning in 1850, Chatin presented evidence that iodine would prevent the development of endemic goiter and cretinism, and following this iodine preparations were used extensively in the treatment of goiter.

In 1904, Kocher, in a long, excellent article, "Die Therapie des Kropfes," presented a study on the effect of iodine in different types of goiter. He gave a summary of the literature, and reported on a special questionnaire which he had sent to his medical colleagues. Kocher emphasized the necessity of a sufficient amount of iodine for the proper functioning of the thyroid gland, and presented conclusive evidence that by its administration many goiters could be made to disappear without harmful effects. The type which he describes as being most successfully treated is the one today classified as the diffuse, vascular, colloid goiter of childhood and adolescence. Some, but not all, of the soft, colloid, adenomatous or nodular types of goiter also reacted well to iodine, and decreased in size without symptoms; on the other hand, the harder, more "meaty" and definitely encapsulated types decreased but little, and very often showed definite symptoms of hyperthyroidism as a result of the administration of the drug. It is this type of case which forms a large proportion of the endemic goiters of Switzerland, and which reacts so badly to iodine, that led Kocher to warn against its indiscriminate use. He emphasized the similarity of

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\* Read before the Association for the Study of Internal Secretions, Chicago, June, 1924.

the resulting constitutional symptoms in these cases to those of Basedow's disease, but refers to a few cases of true Basedow's disease in which the patients appeared to improve after the administration of iodine, and quotes in detail the reports of Collon on Pitres' results from the injection of iodoform. Kocher, however, being influenced by the frequent increase in hyperthyroid symptoms in cases of adenomatous goiter, reconciled the apparently divergent effects of iodine injections in cases of exophthalmic goiter on the ground that the iodine caused atrophy of the glandular substance, or the formation of connective tissue.

In 1910 and 1911 Kocher again discussed at length the use of iodine in goiter. In the first of these papers, entitled "Jod-basedow," he suggests that as iodine is the cause of Jodbasedow, it has a different etiology from true Basedow's disease, and, therefore, is evidence against its being the same disease. Yet this point was overshadowed in his mind by the fact that if sufficient iodine was administered to patients with hard, nodular types of goiter, the resulting symptoms seemed indistinguishable from those of true Basedow's disease, even causing nausea, vomiting, diarrhea, nervousness, tachycardia and rapid loss of weight and strength. It is interesting to note, however, that all of the cases showing ill effects from iodine were of the adenomatous types, and that none was true exophthalmic goiter, although there were a few in which both diseases might have been present. The term Jodbasedow served as a key-note to fix in the minds of all careful workers the danger of iodine in the treatment of adenomatous or endemic goiter; unfortunately the idea went further than Kocher had at first intended, conveying the erroneous impression that it would do harm in the treatment of true exophthalmic goiter. As a result, the use of iodine in all types of goiter was discredited.

Both Albert Kocher and Marine, in their valuable papers on the relationship of iodine to the histology of the thyroid, contributed largely to our knowledge of the subject. The studies of Marine and his associates culminated in the recent demonstration, on the school children of Akron, Ohio, of the prophylactic value of small doses of iodine in reducing the incidence of endemic goiter. In this series the essence of safety, as contrasted with previous efforts at prophylaxis, lay in the fact that the iodine was administered to school children before the de-

velopment of much adenomatous tissue. With regard to iodine in exophthalmic goiter, Marine and Lenhart, in 1911, said: "Drugs have little actual value. Speaking of the almost endless list as a whole, their beneficial influence is determined largely by the mental impression on the patient and by the skill and intelligence with which their use is adapted to each particular case. . . . Iodine has much the same action in exophthalmic goiter with active thyroid hyperplasia as has iodothyreoglobulin, and in addition has the advantage that the dose can be controlled and that the reaction produced depends on the size of the dose and on the degree of the thyroid hyperplasia. We have carefully followed the use of iodine in seventeen cases and have not seen any of the injurious effects commonly described." As a result, Marine concluded that the dangers from iodine in exophthalmic goiter were less than had been supposed. Hare, in his "System of Medical Therapeutics," states that McGuire, in 1881, reported a case of severe exophthalmic goiter in which rapid diminution of the enlarged thyroid gland and a decided amelioration of the other symptoms were obtained by cataphoric treatment with iodine. Chovstek quotes several early case reports indicating a beneficial effect in cases of exophthalmic goiter following the administration of iodine; that there are many such reports in the older literature is hardly to be doubted. Neisser, in 1920, reported seven cases of exophthalmic goiter in which the patients were markedly benefited by the administration of potassium iodide. Loewy and Zondek, in 1921, reported twelve more cases, in three of which the respiratory metabolism was determined and which showed a lowering of the oxygen consumption as a result of the iodine medication.

Neisser and Loewy and Zondek attributed their good results to the small doses of iodine used, and believed that the harmful effects so often warned against were to be explained on the basis of the use of too large doses. It did not occur to them to explain the apparent discrepancies of the action of iodine on the ground that there were two different diseases, because clinicians and surgeons as a whole usually fail to distinguish, at least practically, exophthalmic goiter from adenomatous goiter with hyperthyroidism. At all events, the sequential relationship of adenomatous goiter with hyperthyroidism to adenomatous



goiter without hyperthyroidism is not emphasized by most writers, and the lack of any causal or sequential relationship between exophthalmic goiter and adenomatous goiter, with or without hyperthyroidism, is not stressed. Aschoff and his pupils, however, make a very definite pathologic distinction between these diseases, as was clearly set forth recently in Aschoff's Mayo Foundation lecture.

The first extensive and convincing study of the benefits of iodine in exophthalmic goiter was reported in June, 1923, by Plummer, in a preliminary communication before the Association of American Physicians. His report was based on the careful study, including metabolism observations, of more than 400 patients with exophthalmic goiter, and it showed the great value of iodine in reducing the basal metabolic rate of patients with exophthalmic goiter, in bringing such patients almost immediately out of the dangerous cerebral or gastro-intestinal crisis, and in lowering both the medical and surgical mortality rate. A subsequent report by Plummer and Boothby on more than 600 cases fully confirms the specific controlling effect exerted by iodine in this disease. At the present time (June, 1924) its value has been studied in more than 1200 cases. As yet we have seen no patient with exophthalmic goiter rendered worse by iodine, although the maximal drop in the metabolism is frequently not maintained indefinitely. The most striking and definite effects are obtained in the most severe cases. In twenty-four hours the patient is brought out of the moribund condition, which is associated with the persistent vomiting of the gastro-intestinal crisis of exophthalmic goiter. The effect is as startling and gratifying and fully as certain as that of insulin in cases of diabetic coma. At the recent meeting of the Society for Clinical Investigation, Starr and Means reported a series of cases studied very carefully at the Massachusetts General Hospital, which in every way confirmed our opinion of the value of iodine in cases of exophthalmic goiter. Mason, before the Association of American Physicians (1924), likewise presented essentially similar results, obtained by a detailed study of patients with exophthalmic goiter at the Royal Victoria Hospital in Montreal.

The reader is referred to other articles from the Mayo Clinic with regard to the differential diagnosis of exophthalmic goiter

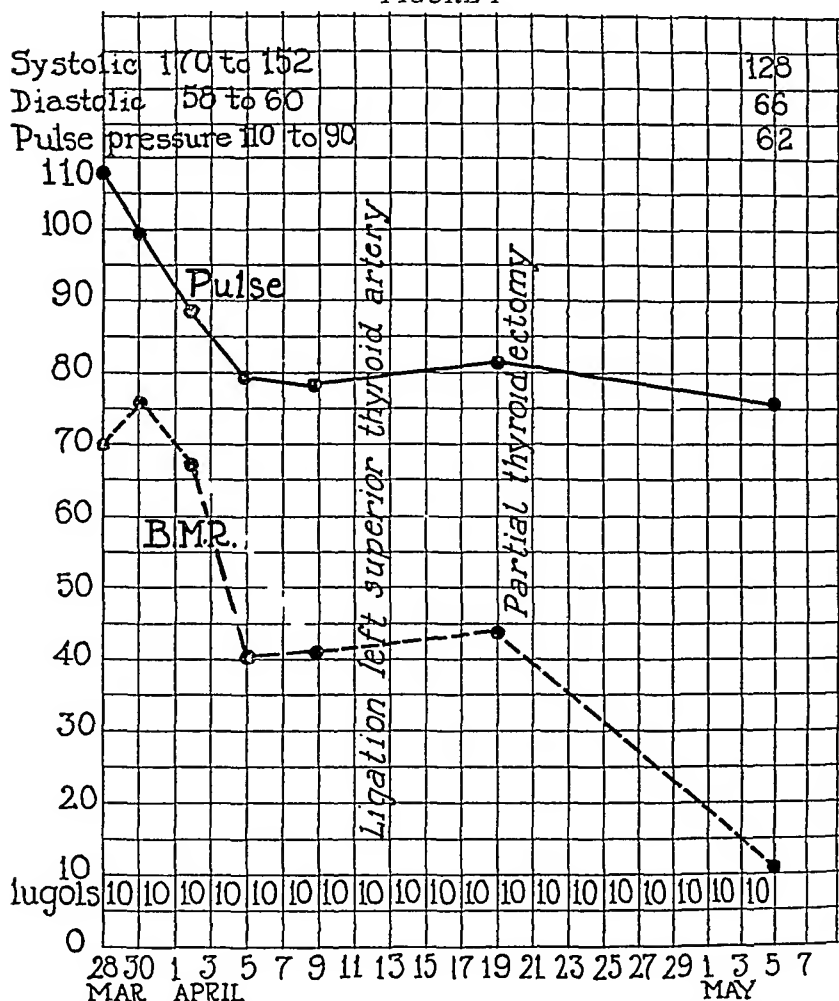
and adenomatous goiter with hyperthyroidism. To prevent any misunderstanding, the following definition is quoted: "Exophthalmic goiter is a constitutional disease apparently due to an excessive, probably an abnormal secretion of an enlarged thyroid gland showing pathologically diffuse parenchymatous hypertrophy and hyperplasia. It is characterized by an increased basal metabolic rate with the resulting secondary manifestations, with a peculiar nervous syndrome and, usually, exophthalmos, with a tendency to gastro-intestinal crises of vomiting and diarrhea. The cause of the altered pathology and activity of the thyroid gland is not known."

Plummer expects to report in detail the theoretic considerations which led to his investigation of the effect of iodine in cases of exophthalmic goiter; I shall not, therefore, discuss this phase of the subject further than to point out that his explanation of the difference in the clinical syndromes of adenomatous goiter with hyperthyroidism and exophthalmic goiter rests on the conception that in the former the constitutional symptoms are due to an excess of normal thyroid secretion in the tissues and cells of the body, whereas in the latter, as a result of an intense and as yet unknown stimulation on the thyroid gland, the quantity of thyroid secretion in the cells of the body not only is increased but that a certain amount of it is imperfect.

In an attempt to modify or improve the abnormal thyroid secretion in cases of exophthalmic goiter Plummer was led to use iodine in the treatment of the disease, on the supposition that the thyroxine molecule was not completely iodized. This supposition is in accordance with certain of the chemical studies of Kendall. The preparation used is that described in the United States Pharmacopeia as liquor iodi compositus, or Lugol's solution; it was chosen somewhat arbitrarily. It contains 5 gm. of iodine and 10 gm. of potassium iodide in 100 gm. of water. In each cubic centimeter of the solution, therefore, there is a total of 126 mg. iodine; in 10 minims 78 mg. or 1.2 gr. The quantity of iodine in this preparation given daily usually varies roughly between 0.1 and 0.3 gm., although as much as 1.0 gm. has been given in one day. We have had but little experience with the use of other iodine preparations; however, it is probable that they would be equally efficacious if the dosage were based on equivalent amounts of iodine.

As soon as a patient with exophthalmic goiter enters the hospital he is started on one or more daily doses of 10 minims (0.6 cc.) of Lugol's solution, depending somewhat on the intensity of the intoxication. Occasionally patients who are in severe crises are given, during the first day or two, as much as

FIGURE 1



Duration 2 months with loss of 40 pounds in weight in spite of good appetite D.E 421157 M.61

100 minims (6 cc.). Subjective symptoms and the nervous manifestations are usually markedly improved within one or two days after starting the iodine. The basal metabolic rate may decrease somewhat during the first week, but the most characteristic drop is obtained about the eighth day (Fig. 1).

When the patient is completely iodized the postoperative reactions are mild. As reported by Pemberton, the surgical mortality rate in the clinic last year (1923) was only 1.4 per cent on the basis of the number of cases. No death occurred from a true postoperative exophthalmic goiter reaction in a series of approximately 1,000 cases in which the patients had been completely iodized before, and during, the operative period. One very instructive case was recently observed.

*Case A456702.* A man, aged sixty-seven years, was admitted to the clinic with the diagnosis of adenomatous goiter with hyperthyroidism. He had been perfectly well until eight months before, when he began to grow weak; he had been obliged to give up work three months before. He had lost weight markedly, had a capricious appetite, and occasionally attacks of diarrhea, but no vomiting. He became nervous and intolerant to heat. His heart became somewhat rapid, especially on exertion; there was no edema, but slight dyspnea. He did not know he had a goiter until he consulted his physician, who prescribed iodine, which produced improvement. On examination a slightly irregular enlargement of the thyroid was noted. There was no exophthalmos, but a slight bruit at the lower right pole. There were tremor of the hands and distinct loss of strength. The basal metabolic rate on four determinations was +58, +51, +64, and +48. As the diagnosis was adenomatous goiter with hyperthyroidism, Lugol's solution was not administered before operation. Thyroidectomy was performed, and the pathologist found two hypertrophic parenchymatous colloid and fetal adenomas in a hypertrophic parenchymatous thyroid. The largest adenoma was 3 cm., the smallest 7 mm., and the weight 28 gm. (the adenomas were incidental). From the pathologic report it was realized that a mistaken clinical diagnosis had been made, that the case was exophthalmic goiter, and that in consequence death might occur from the typical and dreaded reaction of exophthalmic goiter, as the patient had not been protected from this reaction by iodine. For nearly twenty hours he did well, then went rather rapidly into a typical acute postoperative exophthalmic goiter reaction, and died twenty-eight hours after operation.

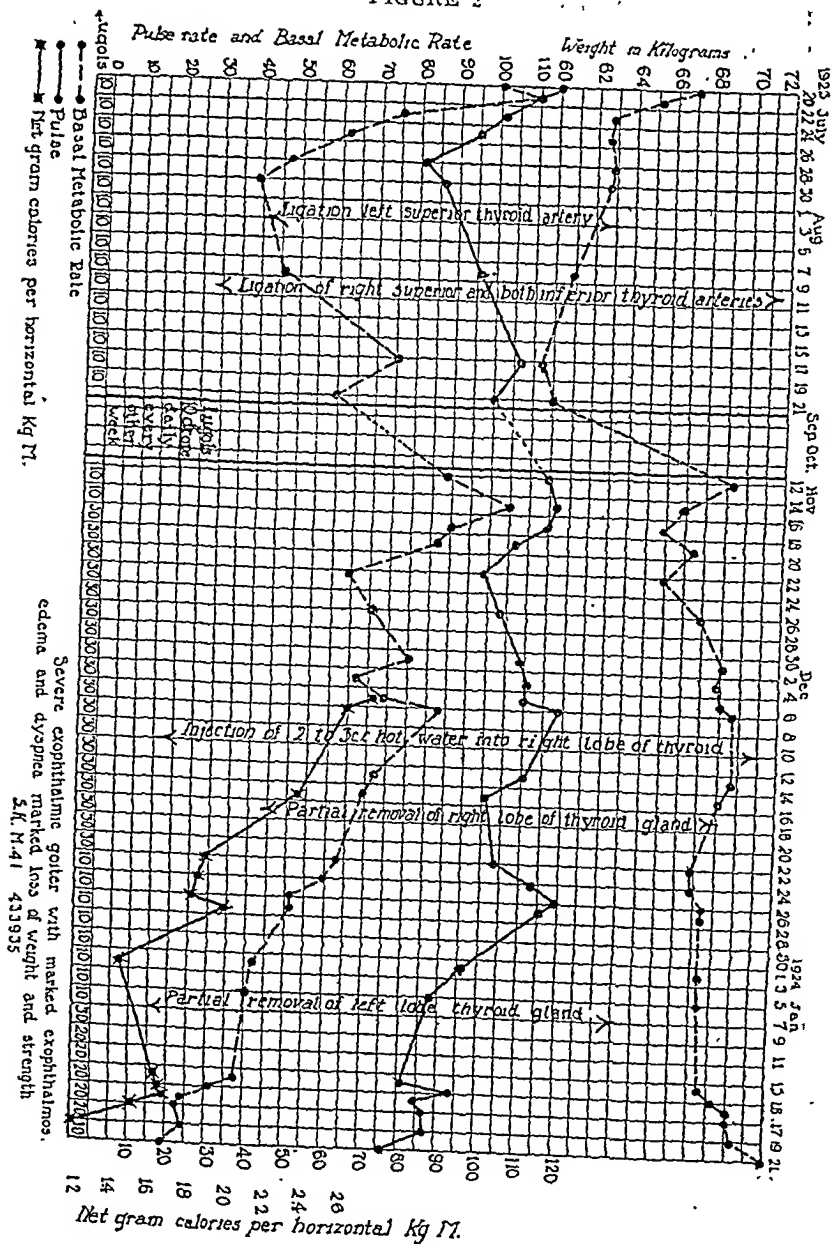
In reviewing the history of this case it can be understood why the mistake in diagnosis was made. The intensity of the

characteristic symptoms of exophthalmic goiter had been reduced by the administration of iodine before the patient came to the clinic, and consequently at the time of our examination there was insufficient evidence on which to base a differential diagnosis. This case emphasizes the necessity of giving iodine immediately before operation in all cases in which there is the slightest possibility of an error in the differential diagnosis, as will be pointed out in more detail later. The main point to emphasize here, however, is the fact that the only surgical death from exophthalmic goiter during seven consecutive months occurred in the only case in which Lugol's solution was not administered at the time of operation, and further, that the death was typical and characteristic of those due to the exophthalmic goiter crisis before the use of iodine in the clinic.

Many interesting points with regard to the effect of Lugol's solution administered over a long period in a severe type of exophthalmic goiter is illustrated by the following case:

*Case A433935.* A man, aged forty-one years, came to the clinic with a history of a very severe but rather short course of exophthalmic goiter. His first symptoms began six months before, with loss of weight and strength; he had not noticed any enlargement of his neck until four months before, when his eyes became prominent. About three months before he became very nervous and tremulous, and for a short period was nauseated and vomited. His appetite then improved and lately has been very large. On examination the thyroid was diffusely and symmetrically enlarged. There were definite thrills and a bruit over the four thyroid arteries, extreme exophthalmos, and marked loss of strength. The heart was moderately enlarged but there were no murmurs. There was considerable edema of the ankles and moderate dyspnea. The patient had the extremely nervous irritability so typical in cases of exophthalmic goiter. The basal metabolic rate was +100 and +110. Lugol's solution was immediately started in daily doses of 10 minims each. As may be noted in Figure 2, there was a progressive lowering of the metabolism; on the tenth day it had decreased to +38, with marked subjective and clinical improvement. On the fifteenth day the left superior thyroid artery was ligated, with very little reaction; five days later the basal metabolic rate was +45. The procedure at this point was de-

FIGURE 2



batable; probably within a few days thyroidectomy, or at least lobectomy, would have been perfectly safe, followed by the second partial lobectomy in about three weeks. However, in conformity with experience previous to the use of Lugol's solution, it was decided that it would be safer to ligate the three remaining vessels. The reaction was moderate. On the seventh day after the second operation the metabolism was +75, and on the twelfth day +60. The preliminary loss in weight of 4 kg. was in part due to the disappearance of the edema, and in part to a partial loss of appetite during the first two or three days; the subsequent loss of weight was due to the decreased amount of food taken during the two operative periods, the latter of which was followed by two days of nausea and vomiting. The patient was dismissed from observation for two and one-half months, taking 10 minims of Lugol's solution daily on alternate weeks. On his return to the clinic his basal metabolic rate had increased to +88 and +105, but he had gained markedly in weight and strength. The Lugol's solution was increased to 10 drops three times a day, following which there was a drop in the metabolism that fluctuated between +64 and +87. Hot water was injected to test the patient's reaction in the operating room, but not for therapeutic purposes, as from our observations hot water injections have never, even slightly, affected the course of the disease. Following removal of about nine-tenths of the right lobe, which was about eight or ten times normal size, there was marked, rapid improvement, as shown by the basal metabolic rate, and also the increase in muscular efficiency, indicated by the lower curve. Three weeks later nine-tenths of the left lobe, about five times normal size, was removed, followed by a very rapid drop in metabolism and restoration of muscular efficiency.

As this case illustrates, slight increase in metabolism is common after the primary decrease, if Lugol's solution is continued for a long time; however, the characteristic nervous symptoms do not recur and the patient remains in an excellent condition. An increase in the dosage may, as in this case, again decrease the metabolism, but such an effect is not certain. If the use of Lugol's solution is discontinued the metabolism almost always increases quite rapidly, with an aggravation of the characteristic symptoms, and the patient may pass into a crit-

ical condition, even into crisis. Therefore, Lugol's solution should not be stopped a few days before, or even on the day of operation; it should be administered regularly throughout the immediate postoperative period. In fact, on the day of operation and on the day preceding and following we have found it advisable to double the regular dose.

During the year, from fifteen to thirty patients with exophthalmic goiter have reached the clinic in severe gastro-intestinal crisis. They were continuously or intermittently vomiting for days or even weeks, with or without having diarrhea. The loss of weight and strength under such conditions is astonishing. The patients not only lose their fat but are dehydrated. They may be jaundiced and are often irrational. The following case is illustrative of this group:

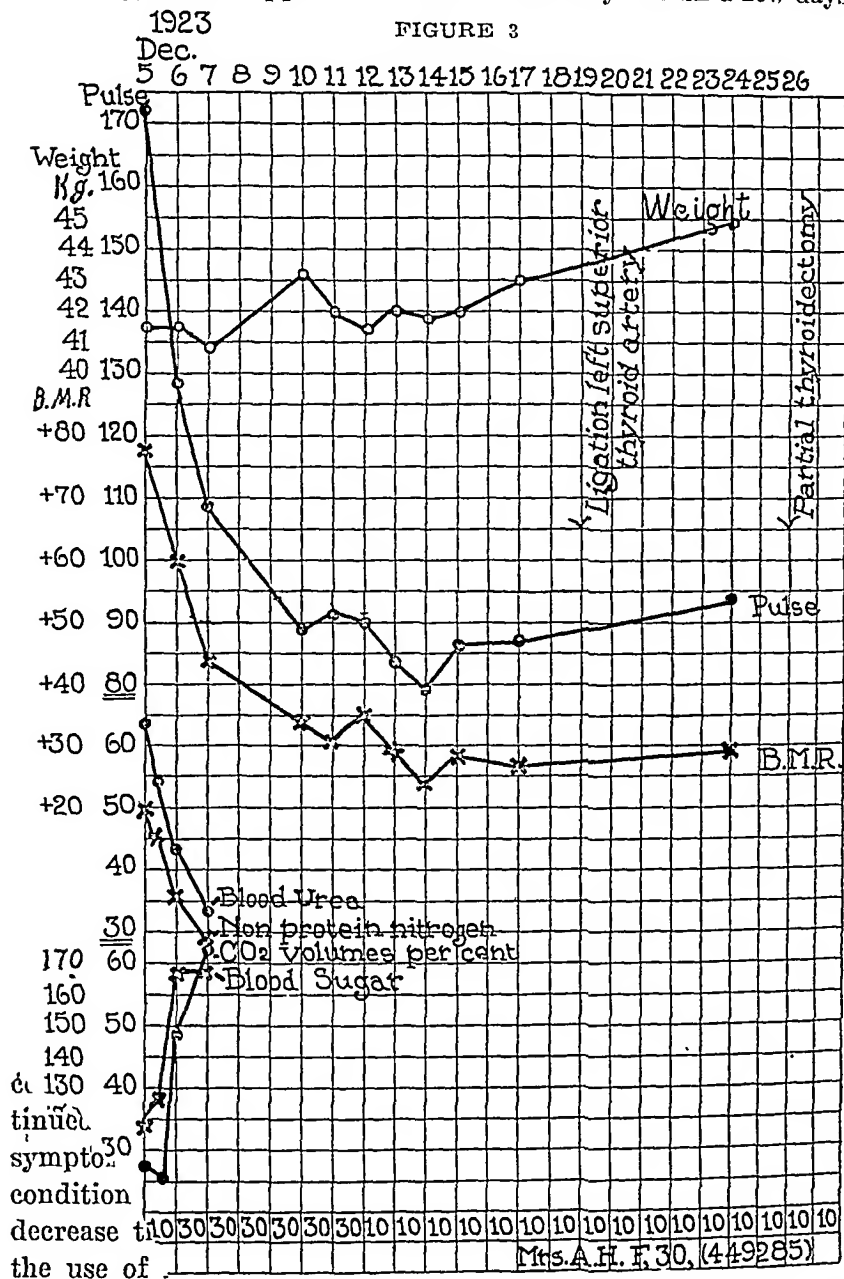
*Case 4449285.* A woman, aged thirty years, entered the clinic in the acute crisis stage of exophthalmic goiter December 4, 1923. She had become nervous and irritable about ten months before. She had not noticed an increase in pulse rate until about six months before, when she became very weak and nauseated, vomited and lost weight. About four months before she had been placed on iodine, and for a time had improved rapidly and gained in weight. The iodine was discontinued, and about five weeks before examination she became much worse than before, her eyes became more prominent and vomiting recurred.

Examination revealed a very acute stage of the exophthalmic goiter crisis with constant vomiting. There were pain and tenderness in the abdomen high on the right side (her appendix had been removed two years previously), suggesting a gallbladder complication. There was practically no increase of temperature, but the leukocytes on the morning of December 5 numbered 29,800, in the afternoon 23,400; on December 6, 7,200, and December 7, 5,200. She had a symmetrically enlarged thyroid, with a bruit over both superior thyroid arteries. During the night and forenoon following admission she became worse, vomiting continued, and there was marked acidosis with a carbon dioxide combining power of 28 volumes per cent. She went into light coma. The urine did not contain sugar, and the blood sugar was normal. There was a marked acetone odor of the breath, and the urine gave a positive test for acetone. During the first twenty-four hours glucose by proctoclysis, and 100



minims of Lugol's solution were administered. There was a rapid decrease in metabolism and pulse rate (Fig. 3). Vomiting stopped and appetite increased markedly within a few days.

FIGURE 3



most always use is interesting since it shows the rapidity with characteristic ss solution will control a dangerous exophthalmic

goiter crisis. For those interested in diabetes the fact is demonstrated that the coma of acidosis can occur when there is no carbohydrate available for burning, as well as when the body is unable to burn it, as in diabetic coma.

The other side of the question, the danger of the indiscriminate use of iodine and the reasons for not administering it to patients with adenomatous goiter, must be emphasized. As has been pointed out, the foundation of the belief of Kocher and others, that iodine is dangerous in the treatment of exophthalmic goiter, and that it may even cause the disease, rests on the fact that they did not succeed in differentiating clearly the various thyroid diseases. In particular they did not separate the syndrome of adenomatous goiter with hyperthyroidism from exophthalmic goiter, except to consider the former a mild or incomplete form of the latter. They failed entirely to recognize that adenomatous goiter with hyperthyroidism is a late hyperfunctioning stage of adenomatous goiter without hyperthyroidism (endemic goiter), and they failed also to appreciate the significance of the fact that exophthalmic goiter is a separate disease entity. The fact that iodine so frequently converts adenomatous goiter without hyperthyroidism into adenomatous goiter with hyperthyroidism, coupled with the evidence that the most characteristic of the exophthalmic goiter symptoms are greatly, and sometimes entirely, relieved by this drug, is one of the most important points supporting Plummer's contention that the two syndromes are separate and distinct diseases.

Many patients who have had adenomatous or endemic nodular goiter for years without constitutional symptoms are rendered hyperthyroid by taking medicine containing iodine. For example, about six months ago a certain district in Minnesota, in which there was a fairly large number of persons with endemic goiters, was well covered by a traveling salesman peddling a "perfectly safe goiter cure." A few months later several patients came to the Mayo Clinic with a typical story of how much they had been harmed by the medicine. The following case serves as an excellent illustration and is exactly like those reported by Kocher.

*Case A455636.* A woman, aged sixty-four years, had worked very hard all her life and taken little care of herself. She had had the goiter for at least fifteen years, but it had never

caused any trouble until after a traveling salesman had sold her some goiter medicine, which she had been taking for six months. Within two months she began to lose weight and strength. The symptoms had been more marked for two weeks, and cardiac trouble developed, as evidenced by tachycardia, palpitation, dyspnea and edema.

The patient presented the typical symptoms of adenomatous goiter with hyperthyroidism. Both lobes and the isthmus of the thyroid were moderately enlarged and somewhat nodular; there were no thrills or bruit. There was no exophthalmos and the eyes did not stare. The patient was somewhat nervous and tremulous, but did not have the typical mental restlessness so characteristic of exophthalmic goiter. Her heart was somewhat enlarged but without murmurs. The pulse rate on admission was 160, but dropped to 100 on the following day. The basal metabolic rate on the morning after admission was +53, and on the sixth day +39. Thyroidectomy was performed on the seventh day after the patient's admission to the hospital. The pathologic report was multiple, degenerating, fibrous, calcareous. colloid and fetal adenomas, weighing 162 gm. The postoperative period was without incident, although the patient regained her strength somewhat slowly.

Such a case is a medical tragedy. Although in this instance the operative procedure, rendered imperative by improper medication with iodine, did not result fatally, yet the patient's general health and cardiac condition were weakened, and she was subjected to a severe strain and considerable unnecessary danger. The operative mortality in adenomatous goiter with hyperthyroidism is now higher than that in cases of exophthalmic goiter.

Although each year we see many cases in which the hyperthyroidism of adenomatous goiter is definitely initiated by the administration of iodine as a "goiter medicine," more cases seem to arise spontaneously. The spontaneous cases may be due to a change in the iodine content of the food or water, because, as pointed out by McClendon and Hathaway, the water of some localities may contain more than 15,000 times as much iodine as that in other places, and the iodine content of the water or food of an individual may vary greatly from time to time, even if he remains in the same place. Or, as suggested by Plummer,

the availability of the ingested iodine may be altered by changes in the gastro-intestinal bacterial flora and their relative affinity for iodine. The cause of the "spontaneous" onset of hyperthyroidism in persons who have had adenomas for many years without symptoms is not known, but may be connected, as indicated, with the average daily iodine absorption which can vary considerably.

Iodine, as has been shown, often definitely initiates the hyperthyroidism of adenomatous goiter, and once the hyperthyroidism is initiated, it rarely shows a tendency to subside, at least completely; on the contrary, in most cases, it seems to be progressive. Iodine, therefore, should never be given in cases of adenomatous goiter without hyperthyroidism.

But what effect does iodine have if given to a patient who already has a hyperfunctioning adenomatous goiter? This question is as yet unsettled. We have seen the hyperthyroidism of adenomatous goiter decrease and certain patients improve after the administration of iodine; on the other hand, certain patients have grown worse, especially if the dosage has been large and long continued. These same results occur if patients do not receive iodine, and the irregularity of results suggests that iodine is principally concerned in the initiation of hyperthyroidism, and that afterward iodine may not greatly alter the course of the disease unless it is long continued. It should be emphasized that possible harm may result, and that further investigation of its effect in this type of case is necessary. We know, however, that in those instances in which the differential diagnosis is not clear it is safe to give 10 minims of Lugol's solution two or three times a day for a week before operation, and for a few days after operation, because during this time no material harm can be done if the condition is adenomatous goiter with hyperthyroidism, and the iodine will protect against the postoperative exophthalmic goiter crisis if the patient has exophthalmic goiter.

One final word of caution with regard to the use of iodine in cases of exophthalmic goiter: There is at present no substantial evidence to indicate that iodine actually cures exophthalmic goiter, although this phase of the problem must be investigated further. The drug improves, and apparently holds in abeyance, the nervous, mental and gastro-intestinal symptoms

which are so characteristic of exophthalmic goiter. It also prevents the development of the fatal postoperative exophthalmic goiter crisis. The metabolism is markedly decreased in about one-third of the cases, somewhat less markedly affected in another third, while in the remainder no demonstrable effect on the metabolism is produced. In general, therefore, according to the evidence available at the present time, iodine should be advised, with few exceptions, only as a temporary therapeutic measure, in the treatment of exophthalmic goiter, to bring the patient into a safe condition for a partial thyroidectomy.

### CONCLUSIONS

1. Iodine administered to patients with adenomatous goiter without hyperthyroidism often initiates a syndrome comprehended in the term "adenomatous goiter with hyperthyroidism."

2. Iodine, administered to patients with exophthalmic goiter, usually reduces the basal metabolic rate, and practically always causes the typical and characteristic nervous and gastrointestinal symptoms to disappear.

3. Iodine, when properly administered, will prevent death from the acute postoperative exophthalmic goiter crisis.

4. Iodine, with few exceptions, should be advised only as a temporary therapeutic measure, in the treatment of exophthalmic goiter, to bring the patient into a safe condition for partial thyroidectomy.

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### DISCUSSION ON PAPER OF DR. BOOTHBY

Dr. Karl Petren, Lund, Sweden: In Sweden we have never seen these gastro-intestinal crises about which we have heard today. We have seen some slight attacks of diarrhea which have caused no harm, but I have never seen these crises with vomiting. So there seems to be some geographical difference in the picture of the disease, for we do not have it in Sweden.

Dr. Russell M. Wilder, Rochester, Minn.: Dr. Boothby's third case presents a very interesting phenomenon, namely, diabetic coma in an individual who is not a diabetic. It further emphasizes the significance of hyperthyroidism, particularly hyperthyroidism crises, in the diabetic—or rather it points out how serious such a condition would be. Glycosuria in patients with hyperthyroidism is not of uncommon occurrence, but real diabetes associated with hyperthyroidism is no more common, I believe, than the combination of diabetes and any other disease. When it occurs it represents a very serious condition. Such a case we had recently; the patient developed a hyperthyroid crisis very shortly after arriving at the hospital. The basal metabolic rate proved to be plus 87. The vomiting and gastro-intestinal symptoms Dr. Boothby described were all present, and an intense diabetic coma promptly developed. One hundred units of insulin a day were ineffective in combatting this diabetic coma, but Lugol's solution was advantageous in correcting it. The situation was so interesting that we could not refrain from trying the effect of removing the iodine. This was done and promptly the basal metabolic rate climbed again, the symptoms of hyperthyroid crisis reappeared simultaneously, and 100 units of insulin were no longer capable of controlling the diabetic condition. The patient was on the verge of a diabetic coma; the iodine was again instituted and the coma was controlled. The case is one of unusual interest because of its bearing on the relationship of hyperthyroidism to diabetes and the effect of iodine in controlling hyperthyroidism. It also illustrates a point made by others, which Dr. Boothby did not mention, that if iodine is instituted in the treatment of these cases of exophthalmic goiter it must not be discontinued, unless very carefully, because if it is discontinued the basal metabolic rate is likely again to rise; in fact, to rise to a higher point than it was before.

and the patient will be in a more critical condition than he was before the iodine treatment was instituted.

Dr. H. Lisser, San Francisco, Calif.: Dr. Boothby made a drastic remark in discussing Dr. Dragstedt's paper, that few cases of myxedema come to the Mayo Clinic correctly diagnosed. We can substantiate that.

It would be a pity if Lugol's solution goes prematurely into general use; toxic goiter is not thoroughly understood, and it does not seem to be as well understood as it should be after all the articles that have appeared on the subject. It may be due somewhat to geographical conditions. Ordinarily in Europe they do not have adenomas as frequently as we have them here, or else this definition is not yet recognized. About ten days ago I came geographically from California to the Mayo Clinic, and I came mentally from Missouri, because I came to see many things, but specifically to find out about Lugol's solution. Dr. Boothby made a preliminary statement in San Francisco a year ago that they were preventing crises by Lugol's solution. I was amazed, because I was under the impression that it was wrong to give iodine to toxic thyroid patients, whether "adenomas" or "exophthalmics." We started it, but not having a clear understanding of what was going on at the Mayo Clinic, we began to think that Lugol's solution would be a cure for exophthalmic goiter. As Dr. Boothby said, it would be a mistake to think we are through with surgery in exophthalmic goiters. This should be stressed: The exophthalmic goiter syndrome that Dr. Plummer and Dr. Boothby have made clear is not the toxic part of hyperthyroidism. We know the toxic part of hyperthyroidism produces tachycardia, tremor, nervousness. I had appreciated that the gastro-intestinal crises are a feature of exophthalmic goiter and not of toxic adenomas, and of course, that exophthalmos, bruit and thrill are present in exophthalmic goiter and not present in toxic adenoma. But I had not realized the very distinct difference in the psychic and nervous phenomenon connected with exophthalmic goiter in contrast to the nervousness and hyperthyroidism in toxic adenoma. These patients with exophthalmic goiter have a particularly distinct intoxication of the central nervous system, as Plummer first brought out. It is in this critical condition that the action of Lugol's solution is almost miraculous. It is so striking that one cannot describe it in any other way.

With Dr. Plummer one afternoon I saw about 75 cases of exophthalmic goiter, and the first thing that struck me and that I remarked upon after I had gone through a few rooms, was the tranquillity of the patients. Here were people with eyes literally popping out of their heads, not a mere von Graefe sign or a Dalrymple's sign; they had not been operated on, yet they were the most placid individuals that you could imagine. After seeing a few I began to say to Dr. Plummer: "This is astonishing; these people are not excited." They still had their tachycardia, not so much, perhaps, but they were composed individuals. Then I learned that apparently the most striking thing that happens besides this very definite action on the metabolic rate is the immediate response when they come in in crisis to considerable doses of Lugol's solution, which is not 10 minims a day—that is given later on—but maybe 70 to 100 minims a day or more. The action is unmistakable, and there is no question that the intelligent use of Lugol's solution is going to do a tremendous amount to lower the mortality in exophthalmic goiter. However, it is not going to stop operation on exophthalmic goiter.

There is undoubtedly a geographical difference. We have plenty of exophthalmic goiter in California and the patients run a high metabolic rate. We get them around 80, occasionally over 100. I

should like Dr. Boothby to say another word about the toxic action on the nervous system. That is something that may have a relationship, though not an exact relationship, to the height of the metabolic rate. You may have a patient with a metabolic rate of 90 or 100, and another patient with a rate of 40 or 50, and the one with the rate of 40 or 50 may be in a far more critical condition than the one with the 90 or 100, because of the toxic action of the abnormal thyroid product on the central nervous system.

Dr. Arno B. Luckhardt, Chicago: What are the chief differential diagnostic differences between exophthalmic goiter and adenomatous thyroid intoxication, and particularly the difference in the sort of nervous irritability seen in the two types?

Dr. Walter Timme, New York: If Lugol's solution is given for a considerable period of time in fairly large doses, does the potassium content of it have any deleterious effect on the cardiovascular system, particularly the myocardium; and if that is the case, would not a sodium solution be better?

Dr. Walter M. Boothby, Rochester, Minn. (closing the discussion): To answer all these questions properly would take a long time, especially the question on the differential diagnosis of exophthalmic goiter. There are a few fairly constant anatomical earmarks of exophthalmic goiter as compared to the adenomatous goiter with hyperthyroidism. Usually in exophthalmic goiter there is a diffusely and symmetrically enlarged thyroid with thrills and bruits and exophthalmos in about 70 per cent of the cases. In adenomatous goiter, with or without hyperthyroidism, the earmarks are different. The thyroid is nodular. Thrills and bruits are no more likely to be found with hyperthyroidism than without. If present they are faint and not over the characteristic superior thyroid vessels. There is one point of confusion. An individual may have had an adenoma buried for years and the thyroid then suddenly develop diffuse parenchymatous hypertrophy and hyperplasia, the surrounding tissue thus developing true exophthalmic goiter.

As to diagnosis, there is a characteristic type of nervousness difficult to describe. It is rather characteristic both in intensity and in type, just as a methyl and an ethyl alcohol intoxication differ in intensity and type. I do not think I can go any farther in the time that is at my disposal.



# THE USE OF IODIN IN EXOPHTHALMIC GOITER

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SAN FRANCISCO

In May, 1923, public announcement was made by Plummer (1) of the satisfactory results obtained with Lugol's solution in the therapy of exophthalmic goiter. During the past year the writer has administered iodine in this form to more than twenty-five patients with results sufficiently interesting to warrant their report, especially since the subject was approached from a different viewpoint than that taken by the Mayo workers.

A review of the early literature on the use of iodine in goiter therapy is contained in a recent article by Plummer and Boothby (2), in which they report the results which they obtained since beginning its use in March, 1922. In the past year occasional mention of iodine has been made by writers reporting on the treatment of exophthalmic goiter, but with the exception of reports from the Mayo Clinic (3) and one by Mason (4) no detailed reports of cases have come to my attention.

The patients to whom I have given Lugol's solution may be conveniently divided into two groups: those previously operated upon and not cured (surgical failures), and those treated solely by non-surgical measures. All the cases in this series (both groups), therefore, received medical treatment while under my observation in contrast to those reported from the Mayo Clinic where iodine was given as pre- and post-operative medication.

Of the twenty-five patients in this series, nineteen had received only medical and Roentgen ray treatment, while six had been operated upon from two to fifteen years previously but still showed thyrotoxic signs and symptoms. Typical case histories (three from each group) will be given. The first three had never had any surgical procedures directed toward the thyroid gland.

I—CASE No. 166. S. F. H., a married woman 28 years of age, was first seen in June, 1923. Her past history was negative and afforded no evident etiology for exophthalmic goitre. Slight "swelling of neck" for four or five years had been noted. Examination revealed

bilateral exophthalmos; Joffroy's sign positive; tremor and uniformly enlarged, soft, vascular thyroid. She complained of loss of weight, nervousness and palpitation. Her basal metabolic rate was plus 42%. Occasional ventricular premature systole was noted. Her subsequent clinical course is shown in Fig. I. With two weeks' bed rest, quinine hydrobromide, and high caloric diet she began to improve and returned to her work. Although the basal metabolic rate dropped and she gained weight and improved in many respects, even to recession of the eyes and diminution of the goitre, she still had palpitation and the basal pulse rate remained at 96-102 for weeks. On November 3rd, she began taking three drops of Lugol's solution once daily in the morning, and by November 10th (in one week), the basal pulse rate dropped to 70. The pulse rate rose again when the iodine was stopped but could again be reduced by resuming it. (See Fig. I.) The decrease in pulse rate was not accompanied by a corresponding drop in the basal metabolic rate, which came down only gradually.

II—CASE No. 643. S. L. H., a female school teacher, 48 years of age, in February, 1923, noticed tachycardia and nervousness. She was confined to bed four weeks with sciatica. Her physician noticed thyroid enlargement at this time. Her past history was negative

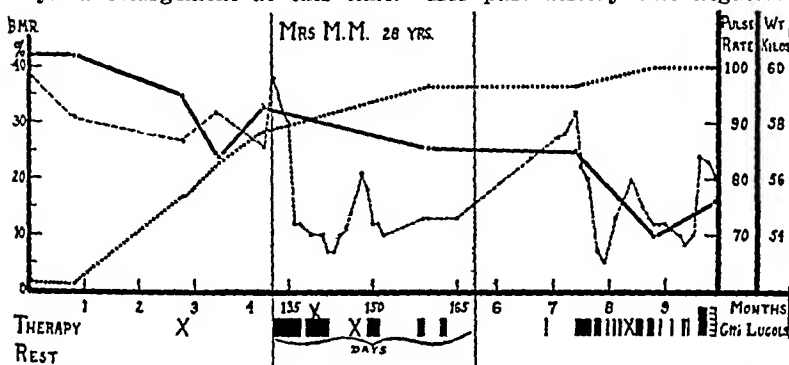


Fig. I. The course, for ten months, of a patient with exophthalmic goiter is shown by the solid line, representing the basal metabolic rate, broken line, the pulse rate and dotted line the weight in kilos. In the row designated THERAPY the X indicates x-ray treatment, and the black areas show dosage of Lugol's solution and the duration of its administration. The simultaneous drop in pulse rate with administration of the iodine is clearly brought out as well as the tendency of the pulse rate to rise when iodine is withheld.

except for "inflammatory rheumatism" at 22. She was examined in a diagnostic clinic in May and a diagnosis of hyperthyroidism (B. M. R. plus 23%) was made. A search for focal infections revealed only cervical polypi and their removal was recommended. She went to a surgeon, who did a hysterectomy in June. Her thyrotoxic manifestations increased and x-ray therapy was instituted. She showed improvement for six weeks and then grew worse. On September 18th the basal metabolic rate was plus 54%. I first saw her on September 24th. She had a pulse rate of 108, a slightly enlarged, soft thyroid, and moderate exophthalmos with considerable puffiness of the lids. Symptomatic treatment with bed rest for two weeks produced improvement, pulse 92, blood pressure S. 122, D. 68. Lugol's solution, five drops daily, was started on October 9th (this was reduced to three drops on October 18th). The improvement was continuous from then onwards as shown by Fig. II, and she began going about. On October 23rd she was struck by an automobile, suffering

lacerations, sprains and a small fracture of the upper ramus of the right pubis. Her discomfort was well borne and the episode did not produce a recrudescence of thyrotoxic manifestations. She remained in the hospital for five weeks and continued to take small doses of Lugol's solution, showing steady improvement. She returned to teaching in January, 1924, continued to gain weight, eyes returned almost to normal, and subjectively she was much improved. On June 2nd, five months after the last recorded rate in Fig. II, the basal metabolic rate was plus 2%.

III—CASE No. 404. S. L. H., a married housewife, 45 years old, in 1915 was treated by a masseur for nervousness and asthenia. In 1916 a tremor developed and by 1917 there was palpitation, profuse sweating, and thyroid enlargement became noticeable. She says she took iodine without any effect. All these symptoms increased in severity until Christmas, 1921. Following the holiday season, during which she worked very hard, her toxic symptoms became more marked and by March, 1922, she had lost forty pounds in weight. She visited

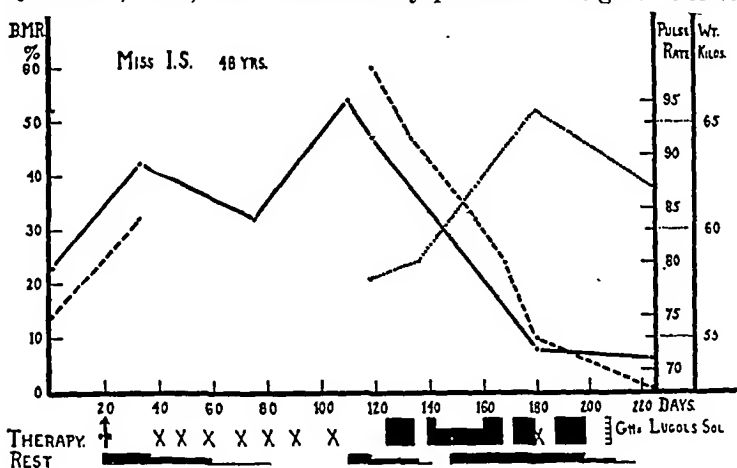


Fig II. The course of a patient with exophthalmic goiter, observed for seven months. Markings on this figure have the same significance as in Figure I. The arrow "OP" at 20 days indicates hysterectomy. The record is incomplete as to weight and pulse rate prior to 120 days, when she came under my observation. Five months after the last rate recorded here the basal metabolic rate was plus 2%.

a physician in April, who made a diagnosis of "goiter." In May she was forced to bed because of weakness and vomiting. She had hallucinations of vision. She first came under my observation on July 21st, 1922, showing extreme emaciation, intense nervousness, and a tremor so marked as to cause her bed to vibrate. She had moderate, bilateral exophthalmos and puffiness of lids; large, soft, vascular gland, the right lobe of which contained a hard mass the size of a walnut. A bruit was heard over the gland. Weakness was so extreme that she was unable to sit without support. Her weight was 110 pounds. The basal metabolic rate was plus 112%; pulse rate 132. She remained in the hospital until September 5th. Fig. III gives the subsequent clinical course. She showed much objective and subjective improvement in the next sixteen months under Roentgen irradiation, but the tremor remained quite marked. Lugol's solution was administered as indicated on the chart. Together with a decrease in pulse rate the tremor disappeared. The patient lived

out of the city and, being possessed of inclinations toward Christian Science, would report only when urged by letter to do so. An endeavor was made to see her at least once a month, and in replies to my letters a very interesting record of the tremor, as it affected her handwriting, was obtained (Fig. IV). The patient is now well and the thyroid nodule is no longer palpable.

The remaining three case reports are of patients who had previously submitted to thyroid operations.

IV—CASE No. 762. A female, nurse, 26 years old, had undergone thyroidectomy at the age of 19 years for exophthalmic goiter. The surgeon reported the thyroid gland to be hyperplastic. She entered training a year later. After training two years she again developed thyrotoxic manifestations. Examination revealed an enlarged left lobe which was thought to be an adenoma and surgery was advised. This was refused so ten Roentgen irradiations were

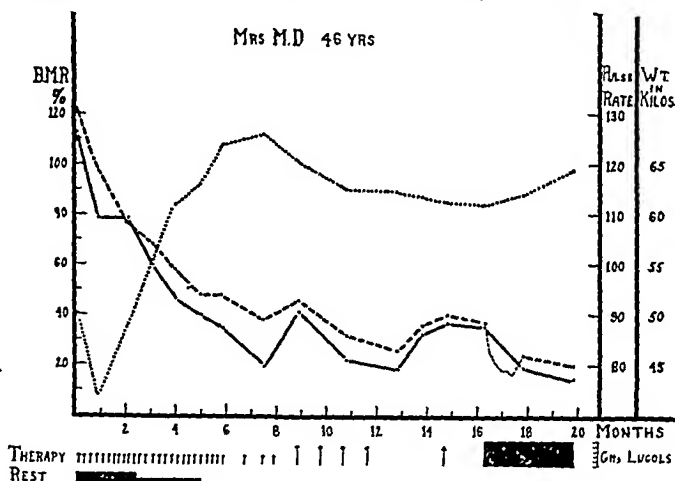


Fig. III. Basal metabolic rate, plus rate and weight in kilos of patient with exophthalmic goiter observed for 20 months. X-ray treatments are indicated in this graph by arrows, otherwise all markings have same meaning as in preceding figures. Lighter broken line of pulse rate between 16 and 18 months is charted from daily morning readings taken after Lugol's solution was started, as indicated in the THERAPY row.

given from August 21st to December 17th, 1920, with abatement of symptoms. The patient remained in the training school and graduated in 1921, though she felt weak and had palpitation. In April, 1922, she was so exhausted she had to remain in bed three weeks. She requested Roentgen irradiations be repeated and these were started May 6th. On June 9th the basal metabolic rate was plus 17%, pulse 98; June 17th, B. M. R. plus 2%, pulse 86. Seven irradiations were given by July 14th, 1922. The patient felt improved and undertook a university course in public health nursing. On February 16th, 1924, she was referred to me by the roentgenologist who had treated her and did not think any more irradiations were advisable. She complained of weakness, insomnia, nervous irritability and irregular, forceful heart action. On examination the pulse was 104, with premature ventricular systoles. She had slight exophthalmos and positive Joffroy's sign. The von Graefe and other eye signs



in April and thyroidectomy in June, 1922. She was better for a while but her old symptoms returned, and in November, 1922, the B. M. R. was plus 33%. She was given some Roentgen irradiations with abatement of symptoms, and on February 19th, 1923, the B. M. R. was plus 17%. She continued to have tachycardia, tremor and nervous irritability for a year, but kept on with her teaching. I first saw her April 12th, 1924, when she showed a pulse of 108: slight exophthalmos and von Graefe sign; warm, moist skin; and slight tremor. There was that peculiar puffiness of the upper and lower lids which is seen in both exophthalmic goitre and hypothyroidism. Her thyroid was not enlarged. Five drops of Lugol's solution, once daily, was ordered. In three weeks there was a decrease in pulse rate to 80, diminution of tremor and nervousness. She lives out of the city and has not had an estimation of the basal metabolic rate, but her physician reports she is much improved.

VI—CASE No. 635. S. L. H., a practical nurse, 42 years old, gave a past history that was negative except for a fibroid operation in 1917. On November 15th, 1919, she had a thyroidectomy preceded by a month's rest in a hospital and treatment on account of a "bad heart." She was apparently improved for she sought no medical attention until September, 1923, when I saw her in consultation. She then presented a picture of intense thyrotoxicosis. There was extreme nervous irritability, marked by incessant movements, dyspnea and marked exophthalmos, greater on the right, with all the other eye signs present. Visible thyroid enlargement and a large, irregular scar which retracted with each inspiration, were noted. There was an absolute irregularity of the pulse though a rate of 160 could be counted at the wrist. Although she was very nervous a fairly satisfactory estimation of the basal metabolic rate showed it to be plus 80%. Her subsequent course is shown in Fig. V. She showed so much improvement under Roentgen irradiations and Lugol's solution that she decided to take her case into her own hands, did not visit her physician, and took up with a cultist whose hobby was "diet and exercise." The diet apparently was harmless, but on the second day of the exercises her fibrillating heart went into acute dilatation and she collapsed. Being ashamed to call her former physician she elected to go to a hospital of her own religious faith. Her condition was precarious; she became unmanageable and caused so much distress to the hospital staff that they had her committed to a state hospital for the insane. There she remained for two weeks before she could convince the asylum authorities of her real condition and was allowed to communicate with her brother. He placed her under her original physician and she entered St. Luke's Hospital with a basal metabolic rate of plus 76%. Lugol's solution was resumed and she was given some more x-ray therapy. She continued quite toxic and at times was irrational and difficult to keep in bed. For the first month there was only a slight change, but during the second month her general condition improved tremendously, with complete return to rationality, decrease in all her thyrotoxic signs and symptoms, and a lowering of the basal metabolic rate to plus 3%.

These six case histories illustrate the effects obtained with Lugol's solution in thyrotoxic patients, half of whom had been previously operated upon. Some of the results are so closely associated chronologically with the giving of iodine that one may assume a causal relationship. Its effect on those signs and symptoms which seem to be caused by toxemia is most marked,

making iodine a valuable addition to thyroid therapy. No patient in this series was made worse by it, eleven showed marked improvement, in eight the improvement was moderate, and in the remaining six the change was slight or negligible. There was one fatality in the group in a patient who came under observation with an auricular fibrillation and a basal metabolic rate of plus 40%. She showed some improvement under rest, digitalis and iodine, and the metabolic rate dropped to plus 12%. She declined to return to a free bed in the hospital when ad-

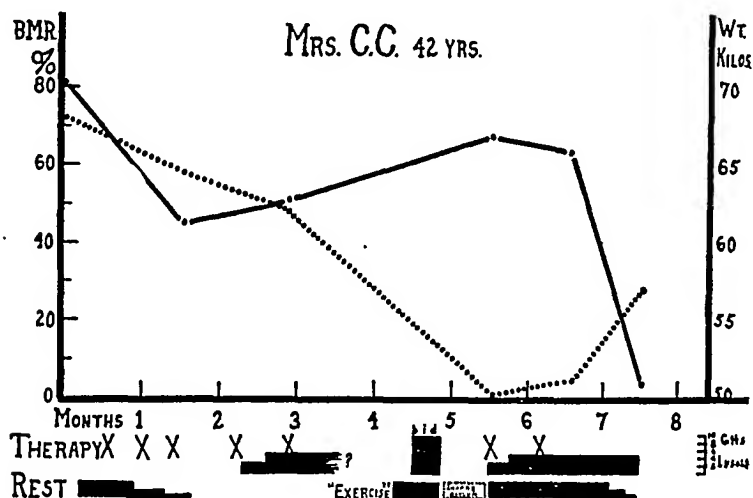


Fig. V. The patient whose course for eight months is shown here had a thyroidectomy four years prior to the time her case was observed as charted. The pulse rate is not recorded because the heart has been in fibrillation since she was first seen. The word "exercise" in the row designated "REST" denotes a period when the patient left her doctor to follow a cultist whose hobby was "exercise." From 3½ to 5½ months she was not under our observation. A basal metabolic rate of plus 161% was obtained at another hospital during this period but is not charted here as it probably did not represent a truly basal rate.

vised to do so, showed signs of mental aberration, and died suddenly with signs of acute cardiac dilatation. Lugol's solution was tried as a substitute for thyroid extract in a case of post-operative myxoedema and a mild rash developed. This promptly disappeared when the iodine was stopped and the patient put again upon thyroid extract, which she had been taking for two years.

A more severe test of the efficacy of iodine in exophthalmic goiter is obtained by those who use it in preparation for operation. The mortality rate at the Mayo Clinic in exophthalmic goiter operations has been reduced almost to nil since Lugol's

solution has been given these patients. Members of the clinic report in detail several cases in which the basal metabolic rate fell to normal before operation, which fact might prompt the question as to the reason for thyroidectomy under such circumstances. The writer is well aware of the frequency of recurrences in this disease, and is also in accord with Barker (5) when he states, "The average duration of hyperthyroidism associated with diffuse hyperplasia of the whole thyroid gland is probably two or three years, no matter how you treat it (medically, surgically or radiologically). You may, it is true, compel a subsidence of the symptoms by treatment, but rarely a cure until the time has elapsed. Moreover, after a recovery from an attack, these patients are prone to recurrence in later life."

In view of the long duration of this disease with its strong tendency towards spontaneous cure after one or more recurrences, which will occur even after subtotal thyroidectomy, one welcomes a therapeutic agent which will produce a remission. This in reality is the most that can be claimed for surgery, x-ray or medical treatment. In those cases which remain cured credit is given to the method employed, but the correct evaluation of therapeutic procedures in this disease is exceedingly difficult.

Since the etiology of exophthalmic goiter is unknown, and since it seems probable that it is not a disease of the thyroid alone but one involving primarily or secondarily the vegetative nervous system, one questions the advisability of ablating an organ which is participating in this interesting symptom complex. The view has long been held by many that the part played by the thyroid is represented by a qualitative rather than a quantitative change in the thyroid secretion. Although Plummer has been an advocate of the "hyperthyroidism theory" in exophthalmic goiter (upon which theory thyroidectomy is based), he states a belief that in this disease the thyroxin molecule is not completely iodized. Kendall's work on the toxicity of the iodine-poor thyroxin molecule supports such belief.

In addition to Kendall's work the observations of Marine also fit into the theory of iodine starvation as a part of the pathological physiology of Graves' disease. Hyperplasia of the thyroid parenchyma is almost constantly present in the



glands of patients with this disease, the degree and amount varying with the severity of the case. Marine (6) has been able to produce thyroid hyperplasia in the dog, ox, pig, sheep and fowl by withholding iodine from the animal and has, in turn, caused a return to normal histological structure by feeding iodine. He states that "When the iodine store was below 0.1 per cent, hypertrophic and hyperplastic changes were regularly found," and believes that "These very simple experiments show clearly that the changes in the iodine store and histologic structure occurring in experimentally controlled hyperplasia are identical with those occurring in spontaneous hyperplasia or goiter." His special interest was in simple goiter, but the hyperplasia here does not differ in its essential details from that in exophthalmic goiter, and the underlying cause of the hyperplasia present in both is probably the same, namely, iodine starvation. In the latter, however, there are other factors concerned, and it has been suggested that the thyroid is only secondarily involved; although the outstanding features of this disease, with the exception of the eye signs, seem to be produced by a disturbance of thyroid function. Iodine substitution therapy seems to be effective sometimes in controlling those manifestations which may be termed thyrotoxic, but it is not to be expected that it will constitute a cure. The problem is not so simple as that. The vegetative nervous system and other glands of internal secretion, especially the sex glands, probably play important roles.

In view of the facts recorded and the theories discussed, it would appear that the thyroid vascularity and hyperplasia of Graves' disease may be a compensatory mechanism just as it is in simple goiter. This suggestion is made in order to explain a phenomenon observed by the writer, recorded by Plummer and Boothby (2), and commented upon by Lahey (7). I refer to those cases which show continued rise in the basal metabolic rate after ligation of one or more thyroid arteries. Such a procedure would seem to constitute a circumvention of nature in her curative endeavors. Surgeons have been unable to explain the event, for ligations have been performed on the theory that the gland is hyperfunctioning and decreasing its blood supply should have the effect of discouraging it in its ambitions. It is probable that the most value derived from pre-

liminary ligations is the time gained, during which a patient often enters on a remission and becomes a better surgical risk. Ligations have not proven of much value to some surgeons reporting their results recently (8), and Mason (3) states, "The day of ligations is over." He further says: "As a means of preparing a case for a primary thyroidectomy, the value of Lugol's solution has been definitely established."

Starr and Means (9) in Boston have had experiences with the administration of iodine in exophthalmic goiter which are similar to those of myself and others. But at this point it may be well to point out that there may be differences in the response to iodine in different parts of the country. For though the symptom complex is apparently the same, the underlying causes may vary. It may be that in goiter districts iodine starvation plays a more important part than it does in non-goiterous areas, and the response to iodine is more satisfactory. A survey of the United States made by McClendon and Hathaway (10) with reference to iodine-poor foods and the goiter districts is suggestive, for they show from the World War draft statistics that exophthalmic goiter was encountered more frequently in the goiter or iodine-poor districts than in the remainder of the country. When this disease occurs in individuals living in Boston or San Francisco, it cannot be ascribed to scarcity of iodine in the food or water. If iodine starvation is the cause, it must be due to some inability of the individual affected to properly mobilize the available supply. Patients with exophthalmic goiter in these non-goiterous districts, however, do improve on iodine, so it may be that by the mass action of relatively large amounts the toxic, iodine-poor thyroxine molecule is converted to a normal or, at least, non-toxic product. Regardless of the theories as to its action it has its place in the therapeutics of Graves' disease, for it has certain definite, measurable effects.

#### CONCLUSIONS

1. Iodine (Lugol's solution) is effective in the non-surgical treatment of exophthalmic goiter.
2. In many cases it produces a reduction in pulse rate, basal metabolic rate, tremor and nervousness. This change is accompanied by a subjective feeling of well being.
3. Its action seems to be quicker in those patients who

have not had any thyroid tissue removed, but even in these patients, some of whom continue to be thyrotoxic, it has proven of definite benefit.

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## SECONDARY SEX CHARACTERISTICS AND THE INTERSTITIAL GLAND

Symposium at the XIX Meeting of the "Association des Anatomistes" at Strasbourg, April 14-17, 1924

REPORTED BY N. GOORMAGHTIGH, GAND.

One of the themes of discussion was the relationship of the secondary sex characteristics and the interstitial gland, of which a brief account is given here.

The chief interest of the symposium centered in a lecture by Bouin and Aneel, who are, as everybody knows, the originators of the widely discussed theory of the interstitial gland.

The aim of previous researches of Bouin and Aneel, on domestic animals, and that of their younger fellow-workers on wild animals, birds, batrachians and fishes, has been to determine what part of the testes elaborates the hormone which controls, as generally agreed upon now, the secondary sex characteristics.

In domestic mammals having a continual sexual activity the sex characteristics remain unchanged or can even develop in the absence of the seminal cells. The latter can be absent in abdominal cryptorchids, or one can cause them to degenerate by ligation of ductus deferens, exposure to x-rays, transplantation, etc., so that in the end there remain only the Sertolian and Leydig cells, the latter as a whole forming the interstitial or diastemic gland.

In such conditions, sex characteristics do not alter. They disappear only when such a transformed testicle is removed. On the other hand, the authors allow secondary sex characteristics to develop despite the absence of seminal cells by destroying these by x-rays in the early stages of prespermatogenesis. The conclusion is evident: the development or maintenance of secondary sex characteristics requires only the presence in the testes of an active interstitial gland and of seminal tubes containing Sertolian cells. Which of these two structures produces the hormone? Bouin calls attention to the compensatory hyper-

trophy sometimes noticed in unilateral cryptorchids. The interstitial gland alone is involved in the process. The Sertolian cells play no part in it. AnceI and Bouin quote also, in support of their views, the curious observations of Lipschütz and his fellow-workers on eunuchoid rabbits with well developed seminal tubes but presenting an atrophic interstitial gland. This seems to prove the importance of the latter gland with regard to the sex characteristics. However, in domestic mammals these striking examples of dissociation of spermatogenesis and interstitial gland activity are quite exceptional. But it occurs naturally in mammals when the sexual activity is periodical.

The problem has been studied by Courier in bats, in which this dissociation of the two glands is very evident. In *Pipistrella*, for instance, seminal tubes are active in summer, at rest in autumn, winter and spring. On the other hand, the interstitial gland is well developed in autumn, winter and spring. The secondary sex characteristics are absent in summer, in full evidence in autumn, winter and spring. This shows clearly that the interstitial gland is responsible for the appearance and development of the secondary sex characters. Moreover, Courier performed sub-epididymal castration in autumn. He then noticed a rapid regression of the epididymis and the glands annexed to the genital tract. Consequently it is the autumn, winter or spring testicle that controls the secondary sex characters. At these periods the seminal glands are at rest, while the interstitial gland is active.

The work of Benoit on birds points to the same conclusions. Destruction of the seminal cells was brought about by x-rays in young cockerels as well as in adults, when at the period of pre-spermatogenesis. The Sertolian cells and seminal cells remain, as do the secondary sex characteristics. The latter begin to develop in young birds while the seminal tubes are still of the embryonic type, so that the presence of seminal cells has no necessary relation to the onset of sex characteristics. This worker has also devoted much attention to the importance of the interstitial cells in birds, some authors having denied their existence. His investigations prove that interstitial cells are at least as numerous as in many mammals. He explains their apparent scarcity by the fact that they are scattered among an enormous

mass of seminal tubes ( $1/60$  of the body's weight, while in man the proportion is  $1/2000$ ). These interstitial cells originate from the seminal cords (confirmation of Nonidez).

Bouin relates also Benoit's work on sex inversion. By castration of young pullets he was able to provoke the appearance of the male sex characteristics and the development of a male gland with spermatozooids, thus confirming Goodale, Pézard and Zawadowsky, but his work is more complete: previous investigators were never able to observe a true transformation of the sex which is characterized in Benoit's experiments by an effective spermatogenesis in some of the newly formed seminal tubes.

Very important work on batrachians was done by Aron. In Anoures and Urodels castration results in involution of the secondary sex characters, at a rate depending on the surrounding conditions. In Anoures, he has studied only the chronological concordance which exists between the seasonal sex character evolution, spermatogenesis and interstitial gland and is able to find a parallelism between the development of secondary sex characters and of the interstitial gland. In Urodels secondary sex characteristics are most prominent in spring, less in autumn, and in complete regression in summer and winter. Now it is just in spring and autumn that the testicle contains, besides the spermatozooids, a special tissue localized at the hilus and recognizable by its bright yellow color. This glandular structure vanishes at the same time as the secondary sex characteristics. Complete destruction of this gland results in regression of the latter as complete as after castration. After incomplete destruction the regression is not so marked. There seems to be a proportionality between the mass of gland and the development of the sex characters. Cauterization of seminal tissues has no influence.

Bouin lays great stress on Aron's investigations because he has been able to perform what is impossible in mammals and birds, i. e., selective destruction of the interstitial cells. His work shows the hormone is produced only by endocrine structures present in the testicle and supports the suggestive observations of Courrier in mammals having a periodical sexual activity.

In fishes the research work is only at a beginning, but Courrier has proved the parallelism of evolution between interstitial gland and secondary sex characteristics.

This important amount of work brings Bouin and Ancel to the following conclusions: the cellular elements of the seminal tubes have no influence on the secondary sex characteristics. The development and presence of the latter depend on a special kind of endocrine cells.

This lecture was followed by discussion which gave opportunity to Champy for giving his own views on the matter. His arguments may be summarized as follows: castration experiments followed by grafts have definitely established the intervention of the testicle in the development of secondary sex characters. The active substance has either a stimulative or a depressive effect (Pézard, Zawadowsky). The genital glands of warm-blooded animals follow an "all-or-none law" (Pézard). Such is not always the case in batrachians and especially in invertebrates, where all sorts of degrees of development of the sex characteristics may exist.

Champy tried to find out what factor controls the volume of the organs influenced by the sexual hormone (sexual variant). It is not the mass of testicular substance, since in partial castration experiments a very small regenerated testicular nodule proves sometimes to be as active as the testes of the controls. The sexual variant is dependent on the state of nutrition. Very fat frogs, increasing steadily in weight, have well developed thumb glands. In thin frogs, on the contrary, they are as small as in total castrates, although the genital glands may have a considerable volume. It must be stated, however, that any development at all of those glands requires a minimum volume of the sexual tissue; but when this minimum is attained the sexual variant depends above all on the state of nutrition of the animal. This observation holds good for the insects where the volume of the sexual variant depends on the size and where, during complete metamorphosis, the amount of nutritive material remains constant. Consequently the problem is an easy one to study. According to Champy, the variation of the sexual appendix in function to the size of the body can be represented by a curve more or less identified with a parabola.

The conclusion is reached that the genital glands act on the sexual variant with constant acceleration. This is in accordance with Pézard's work and with what we know about the way of

action of the thyroid hormone. It favors the idea of a specific catalyser.

Champy considers the localization of formation of the sexual hormone as a matter of secondary importance. Yet he does not agree with Ancel and Bouin. According to him, there are no interstitial cells in appreciable number in the small regenerated testicle nodules at the vicinity of minimum efficacy. In Zawadowsky's and Pézard's experiments, the left atrophic genital gland of the castrated hen develops into a testicle and male characteristics set on at the most different stages of organogenesis of this newly formed gland. Another argument of Champy against Bouin's theory is that some fishes presenting decidedly marked sex characteristics have practically no interstitial cells, while in mammals with a very exuberant interstitial gland the sex characteristics may be absent (mole). With regard to Aron's experiments on poikilotherms, Champy points out the causes of error when the nutritive conditions are overlooked. This criticism of Champy did not remain unanswered. Readers interested in the controversy will find the main lines of it in the "Comptes rendus de la Société de Biologie." It is not possible to give details of it here.

Great interest arose also from the splendid demonstrations of all the material gathered by Bouin, Ancel and their fellow-workers. Whatever may be the truth in this much discussed chapter of internal secretion, the perfect technical value of the documents gathered by the Strasbourg School makes them a unique source of information for those working along the same lines.



# A CLINICAL STUDY OF THE EFFECTS OF MAMMARY GLAND SUBSTANCE UPON UTERINE FUNCTION

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A survey of the literature might lead one to believe that the activity of the mammary gland is in some way related to the menstrual function and that the gland exerts an inhibitory effect upon the ovary.

Briggs (4) says: "Fortunately, in the mammary gland we have a powerful physiologic remedy which either antagonizes or neutralizes the ovarian hormone or inhibits its production or possibly acts more directly on uterine circulation and nutrition." He reports a series of twenty-five cases of uterine fibroids with menorrhagia and metrorrhagia, treated exclusively by mammary extract, hydrastis and ergot. Seventeen of these patients, ranging in age from twenty-six to fifty-six, recovered completely. Emil Novak (11), in discussing this series, says: "I am frank to say that I have never employed this therapeutic agent for such purposes, but I am reasonably sure that it has been similarly neglected by the overwhelming majority of gynecologists and that this neglect is based upon more or less well founded skepticism as to its virtue."

James (9), in reporting ten cases of uterine fibroids treated with mammary extract, ergotin, hydrastis and curetage with successful results, concludes that "there is a definite relationship between the shrinking and disappearance of uterine fibroids and the administration of mammary extract, so much so that, though still inclined to operate in suitable cases, nevertheless I would not condemn the patient to invalidism in case she refused treatment until I had first given the medical treatment suggested. . ."

Von Zelinski (14) reports one case successfully treated after approved methods had been tried and failed—including curetage and the use of styptics. He used five grains three times a day for two periods of two weeks each.

Bandler (1) states: "Mammary extract controls the bleeding from the uterus in many cases, and since its relation to the ovary is undoubted, it is quite possible that by use of the therapy and by diminution of the hyperemia not alone the fibroid will develop less readily but in all probability a retrogressive action is exacted."

While the literature contains many reports similar to the above, we are not aware of any properly controlled clinical study of the problem. Charlton and Lee (5) have recently obtained entirely negative results from feeding mammary gland substance to experimental animals.

In a further investigation of this problem, from a clinical standpoint, we have administered mammary gland substance to women of the reproductive age and made a careful study of the menstrual function before, during and after the experimental period. It was assumed that any hormone that might be present in the mammary gland substance would be most likely to manifest its influence in a detectable way on this function.

Experiments on seventy-nine subjects who gave either normal or abnormal menstrual histories furnish the basis for this paper. Two groups of patients were used: (1) girls selected from the student body of Ohio State University; (2) the highest type of inmates of the State Institution for Feeble-minded at Columbus, Ohio. These subjects were selected at random and their ages varied from fifteen to thirty-three years, the majority being nulliparous, but a few having borne children.

No preliminary attempt was made to classify the subjects as normal or abnormal, in so far as menstrual function was concerned, since we believe that this method of procedure would best serve two purposes: (1) It gives a certain number of normal subjects to use as controls, inasmuch as their general hygiene, school life, working conditions, recreation, rest, diet, etc., are the same as those that presented abnormal menstrual histories; (2) from a practical standpoint, it represents the general average of subjects who present themselves for endocrine therapy.

All patients were first carefully interviewed, and a statement as to their general health and habits was obtained. A careful menstrual history was then recorded. This history included:

the age at which the first menses occurred, its character, the character of the second menses, the menstrual interval, the duration of the menstrual flow and the presence or absence of dysmenorrhea and its relation to the time of flow. In addition to this, a statement was obtained as to the presence or absence of certain disturbances associated with menstruation, namely, general depression, enlargement of the breasts, mastodynia, thyroid enlargement, headache, backache, sensation of weight in the pelvis, bladder irritability, etc. In no instance where the menstrual flow was found to be abnormal was an attempt made to establish the underlying pathological cause, if any.

Following this history each subject was kept under observation for a length of time varying from one to six months, during which period a careful study was made in order to establish definitely the various phenomena listed in the history. This method of procedure established the normal for each individual, as well as ruled out factors such as variation in work, climate, sickness, etc., which at times, and in some individuals may influence menstrual function. After this period of observation, mammary gland substance was administered by mouth to each subject. Ordinary desiccated gland material such as is sold by pharmaceutical firms was used.\* Each grain of this substance represented four grains of fresh sheep gland. The gland substance was given in doses varying from two to eight grains three times a day. The time of administration with reference to the onset of the menstrual flow was also varied. Some subjects received it one week, others two, and some three weeks before the onset, while others were given tablets during the entire menstrual cycle. The gland substance was administered to all of the subjects for a period of one to three complete cycles, after which the administration was discontinued and the same data collected as during the prefeeding and feeding periods. In no case was the subject given any information as to possible effects, and few knew what they were receiving.

The data thus collected may be summarized as follows:

A. NORMAL CASES. Forty-nine subjects (62%) gave a normal menstrual history; that is, there was no evidence of menorrhagia, metrorrhagia, or unusual dysmenorrhea.

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\*For the gland substance used in this work we are indebted to the courtesy of Armour & Co., Chicago, Ill.

During the period in which the gland substance was given: (a) thirty-one of these subjects (63%) showed *no change* in the amount or duration of the menstrual flow; (b) ten subjects (20.4%) showed a *slight decrease* in the amount or duration of the flow; (c) three subjects (6%) showed a *slight increase* in the amount or duration of the flow; (d) three subjects (6%) showed a *slight increase* in the first period after feeding was begun, *followed by normal or slightly decreased* periods; (e) two subjects (4.2%) cannot be classified in the foregoing series. In one of these the flow was lessened in amount but the duration was prolonged. In the other, the flow was absent for a period of two months, followed by a regular interval with a decrease in the amount of flow.

B. ABNORMAL CASES. Thirty subjects (38%) gave abnormal menstrual histories with reference to the existence of menorrhagia, metrorrhagia or dysmenorrhea, or a combination of these.

During the period in which the gland substance was given: (a) nine subjects (30%) showed *no change* in the amount or duration of the menstrual flow; (b) eight subjects (26%) showed a *slight or moderate decrease* in the amount or duration of the menstrual flow or a decrease in the amount of pain; (c) four subjects (13.4%) showed an *increase* in the amount or duration of the menstrual flow or an increase in the amount of pain; (d) five subjects (16.6%) showed a *slight increase* in the amount of flow the first period, *followed by a decrease* in the amount or duration of the flow during the subsequent periods; (e) four subjects (13.4%) gave responses which could not be included in any of the above classes. One subject showed a slight increase the first month after feeding was begun and the balance of the time the amount and duration of the flow were the same as prior to the administration of the gland substance, but the interval varied from two to five weeks. Another subject showed a reduction in the amount of flow and of pain as long as the feeding was continued, but menstruated twice a month following the discontinuance of the feeding. A third subject showed a slight decrease in the duration of the flow, followed by a six weeks' interval, and then reverted to the same type as before feeding. The remaining subject had a flow of six to

Case No.	Before Administration of Gland Substance			During Administration			After Administration		
	Duration of Flow	Amount	Pain	Duration	Amount	Pain	Duration	Amount	Pain
2	7 6 6	S S S	O O O	5	S N N	O O O	4 5	N N	O O
4	3 6 4	N N N	O O O	3 4	N N N	O O O			
5	4 5	N N	O O	8 6	N N	O O			
6	5 5 5	N N	O O	5	N N	O O			
7	6 7	N N	++	6 7 7	N N	+++	7 7	N N	O O
8	3 7	N N	+++	6 3 4	N N	+++	7 5	N N	O O
9	7 6 6 7 7	L L L	+++	4	N N	O			
10	6	N	O	5 4	N N	O	6	N	O
11	4 6 7 6	N	+++	6 5	N N	O O			
12	4 5	N	+++	6 4 4	N N	O O			
13	6 8	N	+++	6 7 6	N N	++			
14	6 7 6 5	N	+++	5 6	N N	++			
15	5 5 7 7	N N	+++	4 4 5	N N	O	5	N	O
16	8 6 7 7	N N	+++	5 8 4	N N	O O	6	N	O
17	6 5 5	N	O	5 5	N N	O O			
20	8 11	N	++	4 4 5	N N	O O	6 7	N N	O O
21	7 7 4	N	O	9 4 4	N N	O O			
22	7 7 4	N	O	4 5 4	N N	O O			
23	4 5	N	O	6 5 6	N N	O O			
24	3 5	N	O	4 4 4	N N	O O	4	N	O
25	3 6 5	N	O	5 5	N N	O O			
26	7 9 7 5 4	N N	++	6 7	N N	O			
27	4 5 8 9 6 13	N N	++	7 9	N N	O			
29	6 6	N	++	4 5	N N	O			
33	3	N	++	8	N N	O			
38	3 6 4	N	++	5	N N	O			
39	5 5 5	N	++	5	N N	O			
43	7 8 8	N	O	5	N N	O			
44	4 4	N	O	6	N N	O			
45	7 9	N	++	6 6	N N	O			
51	7 12 8 5	N	++	7 5	N N	+	5	N	O
52	6 6	N	++	6 3	N N	O			
53	2 3 3	N	++	6 6	N N	O			
56	7 6 5 5	N	O	6 6	N N	+			
57	5	N	+	5 4	N N	+	4	N N N	O
58	4	N	+	4 8	N N	+	4	N N N	O
59	3 11	N	+	8 8	N N	+	4	N N N	O
60	5 5 5	N	O	5 4	N N	+	5	N	O
62	7	N	++	5	N N	O			
63		N	++	6	N N	O			

04	3 4 3	ZZ	+	5 7 3	+	0	N	3	+
05	4 5 6	ZZ	+	7 5 6	+	0	S	5	0
06	1 4 1	N	0	5 5 6	0	0	ZZ	7	0 0 0
07	4 3 4 5	N	0	6 6 7	0	0	N	3	0
08	7 7 9	N	0	3 1 3	0	0	ZZ	7	0 0 0
09	1 3	N	0	6 5 5	0	0	N	5	0
70	5 6 4 1	N	0	5 1 1	0	0	N	1	+
71	4 4 4 1	N	0	1 3 6	0	0	N	6	0
72	6 7 7 5	N	0	8 7	0	0	N	6	+
73	7 7 5	N	0	5 5	0	0	N	6	0
74	4 5 5	N	0	5 5	0	0	N	6	0
75	5 6 5	N	0	5 5	0	0	N	6	0
76	5 6 8 6	N	0	7 6	0	0	N	6	0
77	7 7 8 6	N	0	6 6	0	0	N	6	0
78	7 7 7 6	N	0	6 6	0	0	N	6	0
79	7 7 7 4	N	0	6 6	0	0	N	6	0
80	7 7 7 4	N	0	6 6	0	0	N	6	0
81	7 7 7 1 5 6	N	0	6 6	0	0	N	6	0
82	7 7 7 1 5 6	N	0	6 6	0	0	N	6	0
83	5 7 8	N	0	8 7 7	0	0	N	6	0
84	7 8	N	0	6 6 6	0	0	N	6	0
85	4 5 7	N	0	5 6 6	0	0	N	6	0
86	6 7 1	N	0	5 6 6	0	0	N	6	0
87	6 5 6 6	N	0	5 6 6	0	0	N	6	0
88	6 6 6 6	N	0	5 6 6	0	0	N	6	0
89	2 3 4 1	N	0	5 6 6	0	0	N	6	0
90	7 7 7 7	N	0	5 6 6	0	0	N	6	0
91	3 3 1	N	0	5 6 6	0	0	N	6	0
92	3 3 1	N	0	5 6 6	0	0	N	6	0
93	7 7 8	N	0	5 6 6	0	0	N	6	0
94	5 5 5 9 7	N	0	5 6 6	0	0	N	6	0
95	7 7 7 9 7	N	0	5 6 6	0	0	N	6	0
96	5 5 5	N	0	5 6 6	0	0	N	6	0
97	5 5 5	N	0	5 6 6	0	0	N	6	0
98	6 6 6 1	N	0	5 6 6	0	0	N	6	0
100	8 6 6 1	N	0	5 6 6	0	0	N	6	0
101	8 6 6 1	N	0	5 6 6	0	0	N	6	0
102	3 3 4	N	0	5 6 6	0	0	N	6	0
103	5 7 5 7	N	0	5 6 6	0	0	N	6	0
107	6 7 7	N	0	5 6 6	0	0	N	6	0
111	5 8 6	N	0	5 6 6	0	0	N	6	0
112	6 6	N	0	5 6 6	0	0	N	6	0

Note: Duration of flow in days. S, small amount; N-, less than normal; N, normal; N+, greater than normal; L, large; O, pain absent; +, slight pain; ++, moderate pain; +++ severe pain; ++++, very severe pain.

Remarks  
 Case 7—Interval irregular after feeding began.  
 Case 20—Forty-two day interval after feeding began.  
 Case 65—One period missed when feeding began.  
 Case 112—Severe pain, nausea, vomiting, temperature 101 F., during first period after feeding began.

eight days' duration prior to the administration of the gland substance, normal in amount, but a menstrual interval which varied from twenty-one to forty-two days. Menstrual flow was accompanied by mild uterine colic and slight nausea. The patient received two grains of mammary gland substance three times a day for seven days prior to the onset of the menstrual flow. On the day the flow began she was seized with severe abdominal colic, a temperature of 101 degrees Fahr., nausea, vomiting and marked general depression.

The specific data are summarized in the accompanying table (Pages 766 and 767).

#### DISCUSSION

We recognize the fact that the results obtained in any experimental work involving the investigation on the incretory functions, based upon the feeding of gland substances, are subject to many modifying factors. Some of these, to a certain extent, can be eliminated by the proper selection of control subjects. To this end, it might be stated that the control subjects for this work were living under the same environmental conditions as the abnormal subjects. In spite of this, we realize that controls as well as abnormal subjects may show individual variation.

We also recognize that a pelvic examination of all the abnormal subjects might, in a measure, have been of help in the interpretation of the results which we have obtained, but, on the other hand, we believe that they represent the typical quality of patients as seen by the practitioner and to whom endocrine therapy might be applied by him.

In no instance have we been able to correlate the results obtained with the amount of gland substance administered, neither have we found that the time of administration prior to the onset of the menstrual flow has any effect upon the results obtained.

We also realize that the gland substance which we used may not have contained the active mammary hormone, assuming that such exists. This might be due to some fault in the technic of its preparation or the substance as obtained commercially may vary in its activity, depending upon the state of activity of the glands from which it was prepared.

## CONCLUSION

We are led to believe from the foregoing observations that the effect upon ovarian activity and thus upon uterine function of the feeding of mammary gland substance, as evidenced by changes in the character of the menstrual flow in patients with normal and abnormal menstrual histories, if it exists, is not constant. Neither is it of practical value from a clinical standpoint in abnormal subjects where the abnormality is supposedly due to ovarian hyperactivity, inasmuch as the results obtained were neither constant nor sufficient in amount to warrant its use.

We wish to thank Prof. R. G. Hoskins and also Drs. E. J. Emerick and F. Le G. Keiser of the State Institution for Feeble-minded for their help and encouragement during this investigation.

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# THE EFFECT OF FEEDING MAMMARY GLAND SUBSTANCE UPON THE OESTRUS CYCLE OF THE RAT

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The fact that a physiological relationship exists between the mammary gland and the uterus was somewhat vaguely understood by the ancients, whose simple observations were not obscured by the mass of conflicting experimental data of the present day. Hippocrates (1) wrote: "If in a woman with child, much milk flow from the breasts it indicates that the fetus is weak: but if the breasts be firm, it indicates that the fetus is in a more healthy state." Celsus (2) states that "the nourishment which they (mammariae) draw to themselves passes from the womb (after parturition) to the breasts." It is common knowledge that in late gestation the mammary glands hypertrophy at the same time that the uterus is increasing in size and the menstrual function is suspended, and that during the period of lactation, especially the early part, amenorrhea commonly occurs.

It has often been suggested that such amenorrhea may be due to a hormone elaborated in the mammary cells. This hormone might exert an inhibitory effect upon the ovary and hence affect uterine activity, since the ovary appears to be an important regulator of such activity (3).

It is apparent that there exists a rather definite relationship, either causal or purely coincidental, between the mammary glands and the uterus. There are two possible causal explanations of this relationship: either secretions of the mammary gland may affect uterine activity directly; or secretions of the mammary gland may affect ovarian activity directly, and the ovaries in turn may affect uterine activity. On the other hand, there may be no direct connection between the activities of the mammary gland and the uterus, but both may be controlled by

a factor or factors produced by the ovaries, the ovum, the fetus, or fetal membranes.

The mammary hormone theory derives some support from claims of a beneficial effect from the administration of mammary gland substance to patients with menorrhagia or metrorrhagia. The literature on this point has been considered by Charlton and Rickey (4). This literature is notably lacking in clean cut, convincing data. It seemed desirable, therefore, to subject the theory to experimental study under controlled conditions.

#### METHODS

Albino rats (*Mus norvegicus albinus*) of breeding age were selected as experimental animals, both because of the ease with which they can be reared and cared for and because of the definiteness of our knowledge of their uterine activity.

In 1922, Long and Evans (5, 6), extending the observations of Stockard and Papanicolaou (7) on the guinea pig, described a method of following the oestrus cycle in the rat. They have shown that there is an orderly and step-like series of changes in the epithelial layers of the vagina which produces a definite succession of cell types in the vaginal fluid, and that a microscopical examination of this fluid constitutes a reliable method of recognizing subdivisions of the oestrus cycle in the living animal.

Long and Evans have distinguished five stages in the cycle. The average length of the cycle is between four and six days, about one-half of this time being occupied by the so-called quiescent period or pause (dioestrus interval) or Stage V. The other half comprises the more active stages and is associated with oestrus and ovulation.

The oestrus they have divided into four stages. In *Stage I*, the preparation for oestrus, the smears show nucleated epithelial cells only; the cells are not, or are only slightly, cornified. The mucosa is dry and opaque. The cells are somewhat granular. This stage is of about twelve hours' duration.

In *Stage II*, the stage of uterine hyperemia and distension, the ovarian follicles reach their maximum size. The smears show

The daily study of vaginal smears was, of course, continued throughout the experimental period. The observations in both the experimental and control animals are set forth in the accompanying tables.

TABLE I. SHOWING DURATION IN DAYS OF OESTRUS CYCLES IN CONTROL RATS

Rat Number	Lengths of Successive Cycles in Days	Mean No of Days per Cycle	Standard Deviation $\pm$
1416	8, 5, 4, 5, 5, 5, 5, 6, 5, 5	5 30	1 004
1513	5, 5, 5, 4, 6, 4, 8, 5, 5	5 22	1 13
1516	6, 5, 7, 6, 5, 6, 7, 6	6 00	0 70
1413	7, 5, 6, 6, 8, 7, 6, 4, 6, 5, 5	5 90	1 08
1019	5, 5, 5, 6, 4, 5, 5, 3, 3, 4, 6	4 63	0 97
1700	6, 5, 5, 6, 7, 5, 4, 5, 5, 6, 5, 4	5 23	0 79
1400	4, 5, 5, 6, 4, 7, 5, 5, 8, 7, 6, 6	5 66	1 17
1600	5, 4, 6, 6, 6, 4, 4, 4, 5, 5	4 90	0 83
1213	5, 6, 6, 5, 4, 8, 6, 4, 5, 1, 5, 5	5 25	1 08
1415	5, 5, 6, 5, 4, 4, 4, 5, 4, 6, 6	4 90	0 78
Mean Number of Days per Cycle		5 30 Days	
Standard Deviation		$\pm 1 05$	

TABLE II. SHOWING DURATION IN DAYS OF SUCCESSIVE OESTRUS CYCLES IN RATS FED MAMMARY GLAND SUBSTANCE

Rat Number	Preliminary Observation Period	Mean	Period of Feeding Mammary Gland Substance	Mean	Final Rest Period	Mean
1115	6, 5, 6	5 6	4, 6, 6, 5, 4, 5, 6	5 1	6, 5, 5	5 3
1011	6, 4, 6	5 3	6, 7, 4, 4, 6, 5	5 3	4, 6, 5, 5	5 0
1000	5, 6, 4	5 2	6, 5, 5, 5, 5, 4	5 0	5, 4, 6, 6	5 2
1214	5, 4, 6	5 0	5, 6, 6, 6, 6, 5	5 7	4, 6, 4, 5	4 8
1016	5, 7, 6	6 0	7, 5, 4, 4, 5, 5	5 0	5, 6, 5, 5	5 2
1012	9, 4	6 5	6, 5, 6, 5, 5, 5, 6	5 4	6, 5, 5, 5	5 2
1112	5, 5, 5	5 0	5, 5, 6, 5, 5, 4, 6	5 1	5, 5, 5	5 0
1117	4, 5, 6	5 0	6, 5, 5, 5, 5, 5	5 2	5, 5, 5, 5	5 0
1100	6, 5, 5	5 3	6, 5, 4, 5, 5, 6	5 2	5, 5, 5, 5	5 0
1015	4, 5, 6	5 0	5, 6, 4, 5, 5, 5, 5	5 0	5, 5, 4, 5	4 8
1215	6, 5, 5	5 3	5, 5, 5, 5, 5, 6, 5	5 1	5, 5, 5, 5	5 0
Mean		5 36 Days	5 19 Days		5 04 Days	
Standard Deviation		$\pm 1 010$	$\pm 0 223$		$\pm 0 533$	

These data may be summarized as follows.

1. Both the control and experimental animals during the period of preliminary observation showed oestrus cycles, the total duration, as well as the length of component stages of which fell within the established normal limits.

2. In no instance was any effect of the mammary gland

feeding apparent. No significant differences appear between the cycles of the experimental and the control animals or in the experimental animals between the preliminary, the feeding, and the after periods. Both total cycle lengths and duration of component stages were considered. The regularity of the cycles of the control group throughout the course of the experiment indicates that no extraneous environmental disturbing factors entered in.

#### DISCUSSION

The supposition that the mammary glands produce a hormone is based primarily on the observation that disturbances in the oestrus or menstrual cycle coincide with periods of mammary activity. The therapeutic use of mammary gland substance postulates an artificial augmentation of such a circulating hormone. The results herein reported indicate that no such effect can be secured. The results throw further doubt upon the theory of a mammary hormone, although they do not conclusively disprove it. The possibility remains open that the hypothetical hormone may be destroyed in the manufacture of the gland product, or that the hormone is destroyed by the digestive juices when administered by mouth. In all experiments of this sort negative results are necessarily inconclusive, but in this, as in similar cases, such results cast an added burden of proof upon the proponents of the hormone theory.

It should be noted that the amount of mammary gland substance administered to each rat would correspond to a daily dosage of two to four ounces of desiccated material in the human being.

We wish to acknowledge our indebtedness to Professor R. G. Hoskins, under whose direction these experiments were performed.

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or arranged as definite acini around a lumen which may contain colloid. The oxyphile cells are fewer in number than the chief cells, and are said to be much like the eosinophiles of the hypophysis. They occur in the same groupings as the chief cells. Pool's article (1907) does not add much to Welsh's description.

Bergstrand (1920), also studying the human gland, considers that the chief cells are the only cells of functional value, and the Welsh's cells are a degeneration product. He finds colloid in the gland, which may be a true secretion or may represent further degeneration of the Welsh's cells. Koopman, on the other hand (1921), from a study of 255 cases, comes to the conclusion that the acidophile cells are the morphological expression of the internal secretory activity of the gland. He believes them to be very much like the eosinophiles of the hypophysis, and observes that their number increases with age of the individual. He also distinguishes two kinds of acidophiles, light and dark red.

As regards histological changes due to age and difference between sexes we have only a few observations besides those of Koopman. Bjure (1918), working with rabbits, has made an extensive study of growth and of the alterations of the relative amounts of connective tissue and parenchyma. He finds that the parenchyma is 97 per cent of the organ at birth, falls to 89 per cent at the second month, and rises to 92 per cent at the fourth month. He has also plotted the weight of the whole gland on the age of the animal, showing the relative size to be greater in females than in males. This is in accordance with Jackson's observations on rats (1916). He finds the parathyroid of female rats to be relatively larger than that of males, and notes that the structure is essentially the same at three and at ten weeks.

#### MATERIAL AND METHODS

The present paper deals with the histology of the parathyroid and the effect on it of pregnancy, diet, and differences of age and nervous condition. It was found from a preliminary survey of material from four different sources that a variation in the technique of dissection and fixation produces very striking differences in the appearance of the parathyroid. The ma-

terial at first studied included specimens from the Wistar Institute, the University of Minnesota, and the College of Agriculture of the University of Arkansas, as well as those from our own colony at Little Rock. It was found, however, that the parathyroids in the first two groups had undergone post-mortem changes, and they have been for the most part excluded from the present account. The material from the Agricultural College and from our own colony was prepared in such a way as to prevent these changes.

The animals used were ordinary stock colony rats of various ages. The Little Rock group had been fed on corn meal, oats, wheat, and a mixed chick feed, together with a liberal supply of fresh milk, bread, and lettuce or raw cabbage. A few had also been given raw meat. The animals from the Agricultural School had been fed on a special balanced ration prepared by Dr. Barnett Sure of that school. They were exceptionally well grown, having weights far in excess of those from any colony with which I have dealt.

For all material which was prepared in the University of Arkansas laboratories the following technique was used: The trachea and esophagus with the thyroid and a little of the adjacent muscular tissue were dissected out and fixed together. Later, when the material had been hardened in alcohol the thyroid and parathyroid were separated from the other parts and embedded in paraffin. This method eliminates the postmortem changes which occur when the thyroid is dissected off the trachea and weighed before fixation.

The tissues were embedded in paraffin or in a mixture of paraffin and bayberry wax, and cut at various thicknesses. The majority were fixed in Bouin's fluid and stained with Delafield's hematoxylin and eosin. This technique is satisfactory for general purposes. Some special methods, such as Bensley's mitochondrial technique have also been used.

*Histology:* 1. Parenchyma—Three types of cells have been observed in the parenchyma of the parathyroid of the albino rat.

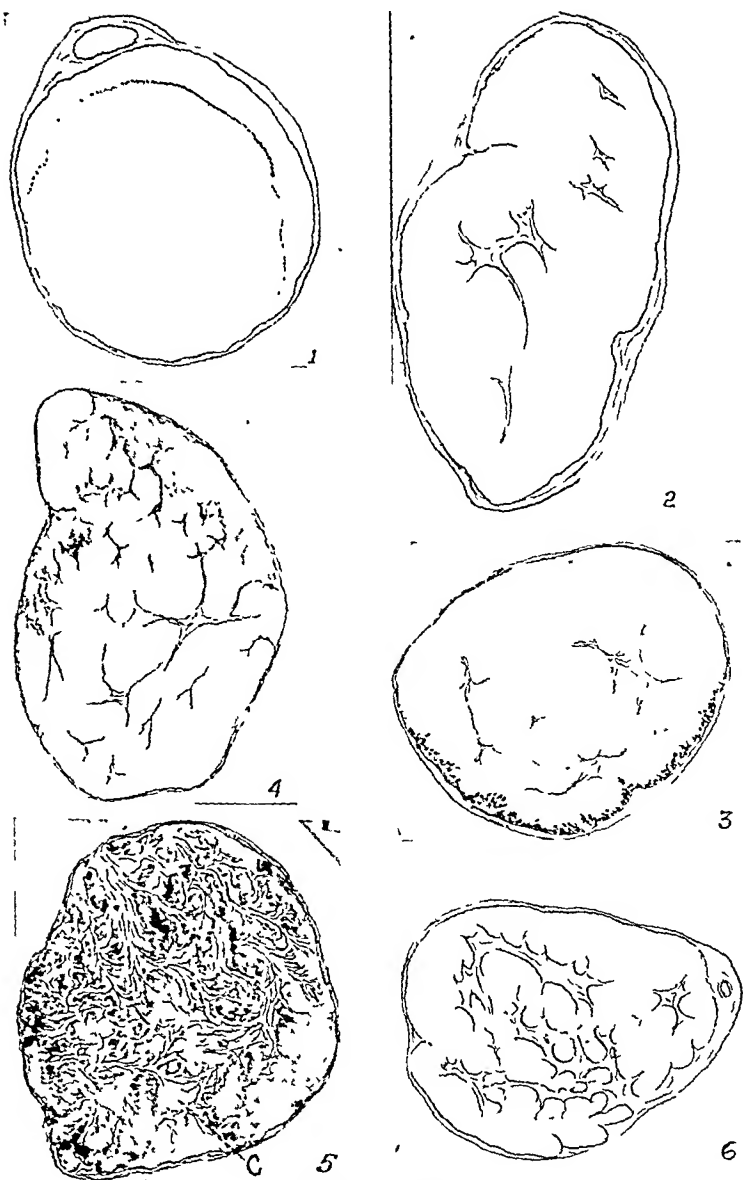
(a) Chief cells. These make up the greater part of the parenchyma. They are polygonal cells with vesicular nuclei. In ordinary sections the cytoplasm is not noticeably granular, and the cell walls are indistinct. When Bensley's technique is

used the chief cells appear granular and the cell walls become very clear. This type of cell is illustrated in Figure 1 (Plate I), and in practically all the other figures, and corresponds to the chief cells described by others in the human parathyroid. They may fill the whole gland in a homogeneous mass, with fibroblasts and strands of connective tissue among them, or they may be grouped in rounded masses or in anastomosing cords separated by strands of connective tissue. Acini or follicles have not been observed in this material, nor has colloid been found in it.

(b) The second type of cell observed in normal rat material is the light-colored peripheral cell illustrated in Figure 2. This has the same staining reaction as the chief cell, of which it is probably a modification. The difference between the two types is in the cytoplasm, which is paler and more extensive in the peripheral cells. The cell walls are more distinct in them than in the chief cells. They are most often seen forming a narrow zone around the outside of the gland as in text Figure 1, but they may form a large part of the organ, leaving only a small area of the darker chief cells (Text Figure 2).

(c) The third type of cell to be found in the parathyroid of the rat is that which we called the chromophile cells in our preliminary report on this work. These are smaller than the chief cells and have dark nuclei almost solidly filled with chromatin. They take a counter stain deeply if it is at all strong, but in the absence of eosin they are darkly colored with hematoxylin. When strongly stained with eosin they are not scarlet like eosinophilic blood cells, but a deep reddish purple without noticeable granules. Other investigators have described eosinophiles in the parathyroid which are identical with the eosinophiles of the hypophysis. But the cells just described are not true eosinophiles and do not have any counterpart in the hypophysis of the white rat. They sometimes form a thin zone at the periphery of the gland on the side nearest the surface of the thyroid. From this region they seem to invade the gland so that at times a whole section is composed of them. They are illustrated in Figure 3 (high power) and their distribution in the gland is shown in Text Figures 3, 4 and 5.

2. Connective Tissue—The parathyroid is always separated from the thyroid by a fibrous capsule and varying amounts



TEXT FIGURE

1. Narrow peripheral zone of light cells
2. Light cells composing the greater part of the gland
3. Narrow zone of chromophiles, with light cells beneath
4. Chromophiles spreading inward from the exposed edge of the gland
5. Chromophiles composing the entire parenchyma except for small islands of chief cells (C).
6. Gland with large islands of connective tissue.



of connective tissue are present throughout the gland itself. In some cases there are no strands of fibrous tissue visible under the low power of the microscope, but fibroblasts may be seen on closer examination, and fine, isolated fibers. In other instances larger strands and islands of white fibrous tissue are to be seen cutting the parenchyma in various directions. This last condition is illustrated in Text Figure 6.

Cells are sometimes present in the connective tissue which may be called true eosinophiles. They have a large cell body conspicuously filled with scarlet granules. The nucleus is pyknotic. These have been found only in the material coming from the University of Minnesota. Cells of a similar size, shape and position have been seen in the specimens from our own colony, but here the staining reaction is different. In our specimens the cells have a basophilic reaction or have the lavender color of neutrophilic leucocytes. The basophiles show a less pronounced pyknosis, and the neutrophiles a clearly vesicular nucleus. These cells are not confined to the parathyroid, but may be found in the connective tissue surrounding the thyroid follicles and in the connective tissue of the thymus and lymph nodes of the neck region. We have not found them in sections of hypophysis, spleen, kidney or liver. The eosinophiles are illustrated in Figure 4, the basophiles in Figure 5.

*Discussion of Types of Cells:* The chief cells are, in our opinion, the only functionally important type in the parathyroid of the rat. They are the only kind present in all specimens, and in the great majority of cases the entire parenchyma is composed of them. To suppose they are not functionally important one must assume that the gland is inactive in most of the material we have examined. The experimental work described below substantiates the belief that no other type of cell furnishes an index of the activity of the parathyroid.

The cells of the light zone, since they have the same staining reaction as the chief cells, are probably a modification of the latter. They are not senescent cells, since mitoses are often present in this zone. It is more probable that they represent a region in which rapid growth is taking place. Tanberg (1916) notes what must be similar cells in cat parathyroids which are undergoing hypertrophy. He describes them as large transparent cells with eccentric nuclei, rich in chromatin. It is pos-

sible, however, that the light zone is the result of some slight variation in technique and is quite without functional significance.

The chromophile cells are unquestionably the result of postmortem changes. It was at first supposed that their appearance in one group and absence from others might be due to some difference in the environment of the stock. But experiments with material from our own colony have shown that the dark cells do not appear as the result of any change in the surroundings of the colony. They appear, however, in material which has been dissected out and kept under a glass jar for some time before it is fixed. Chromophiles are conspicuous in specimens from the Wistar Institute and from the University of Minnesota, and all of these had been carefully dissected and weighed. They must, therefore, have been out of the rats from which they were taken for some time before they were fixed, giving an opportunity for postmortem changes to take place. The character and distribution of the cells is such as to support the belief that they are the result of drying or pinching. As we have said, they make their first appearance at the outside edge of the gland where it is not covered by the thyroid, and spread inwards from that position. Material from the Wistar Institute prepared according to our technique shows no chromophile cells.

The eosinophilic and basophilic cells found in the connective tissue are to be classed as plasma cells rather than as cells belonging particularly to the parathyroid, since they may be seen in the connective tissue of other organs in this region. It seems most unlikely that they have anything to do with the function of the parathyroid.

#### COMPARISON WITH CAT AND HUMAN MATERIAL

After we had determined the source of the dark cells of the parathyroid of the rat the question arose whether these correspond to the eosinophile cells described in the human glands and in those of the cat. Parathyroids from eleven cats were examined and compared with the rat material. As may be seen from Figure 6, the chief cells of cat parathyroids are essentially like those in the rat, but their arrangement is somewhat different. Follicles, which we have never found in rat

material, are not infrequent in cat parathyroids. There is a considerable amount of connective tissue arranged in fine strands, but we have not found specimens with large areas of fibrous tissue in them. We found that if the glands are subjected to drying, as those of the rat had been, the chief cells were transformed into dark cells with pyknotic nuclei which are similar in every essential to the dark cells of the rat parathyroid.

These are not, however, the eosinophiles described by Welsh. In one gland from the forty-four examined we found a group of cells which correspond to his description of eosinophiles. These are illustrated in Figure 7. They are much larger than the chief cells and have a granular cytoplasm stained a pale red in this specimen. There is no mistaking these cells; after seeing a group one is convinced that he could not possibly overlook them in any other specimen.

We have obtained only two sets of human parathyroids in this laboratory, but one of these shows very striking eosinophiles, illustrated in Figure 8. It may be seen from this figure that the chief cells of the human parathyroid are not exactly like those of the rat. The most noticeable difference is that the cytoplasm is more vacuolated and the cell walls more prominent. However, as neither of our specimens was from a perfectly healthy individual, they may present conditions which are abnormal. The eosinophiles figured are comparable to those of the cat, but they took the stain more deeply and uniformly. They show the striking similarity to the eosinophiles of the hypophysis, which has been noted by Koopman.

Our study of the parathyroid of the rat does not yield positive information as to the conditions which lead to the presence of Welsh's cells, since such cells are not found in the rat at all. We may point out, however, the following facts which make us doubt that these cells are the functional cells of the gland. Whatever may govern their appearance in human beings, they were found in a very small proportion of the cats only one out of eleven specimens. The cats were vagrants of various ages, both sexes, and different conditions of nutrition. It is hard to believe that the other ten cats had non-functional parathyroids; and impossible to think that the gland was not active in any of the hundreds of rats examined by us. We are

obliged to conclude either that the parathyroid of the white rat has not the same function as that of man, or that the eosinophiles are not the most important cells of the human parathyroid.

#### EFFECT OF VARIOUS CONDITIONS ON THE HISTOLOGY OF THE PARATHYROID

1. *Age Changes:* Since the susceptibility of the rat to tetania parathyreopriva seems to vary with age our material has been scrutinized with particular care to see if there were a corresponding morphological change. Animals have been selected at the following periods: New-born, twenty-one days, thirty days, fifty days, seventy days, and one hundred and fifty days. The changes observed are in the number of mitoses, rather than in the character of the cells themselves. Mitoses are frequent in the parathyroids of the new-born rat, the count running as high as forty-five figures in a small gland. The condition of active cell division persists through the nursing period. Specimens killed at the age of twenty-one days still show many mitotic figures. By the time the rat is thirty days old, mitosis has greatly decreased, and it is only in exceptional cases that more than four or five figures are to be found in specimens of this age. The exceptions are the glands of rats which are noticeably undersized. These show also a type of arrangement of the cells which is like that of the younger specimens. Apparently a second period of active mitosis occurs some time between fifty and seventy-five days. As fifty and seventy-five days were the periods originally selected for our study we have only a few specimens falling between these ages. Several of these, however, show a marked increase in mitosis. Further study will show whether there is a marked increase in the size of the gland occurring regularly at this time.

The arrangement of the cells changes gradually with advancing age from an indefinite one to a fairly definite organization into cords. This goes along with a gradual increase in the fine strands of connective tissue lying between the cords. The two conditions are illustrated in Figure 9 (new-born) and 10 (seventy-five days). The change usually begins between the thirtieth and fiftieth days; the arrangement is seldom seen in thirty-day specimens and usually found in fifty-day ma-

terial. The fine strands of connective tissue increase with age, but the presence of large masses of fibrous tissue seems to be independent of this factor. The condition occurs in occasional cases from thirty to one hundred and fifty days. So far we have not correlated it with any factor of the environment.

2. *Nervous Condition:* The results obtained by Dr. Hammett indicate that the susceptibility of the rat to tetania parathyreopriva varies according to the nervous condition of the animal. In a series of operations he found the mortality to be 78 per cent among ordinary stock rats and only 13 per cent among gentled rats. We have studied histologically the parathyroids of gentled rats, comparing them with those of stock rats and also with those of wild gray rats which we caught in wire traps. In a preliminary report (1923) we stated that the parathyroids of gentled rats show areas of hyaline material which we believed to be a sign of degeneration of the parenchyma. After further investigation of the matter we are convinced that the areas are extravasated blood. A larger number of specimens show no such changes. The parathyroids of gentled rats are not to be distinguished from those of ordinary stock rats. Furthermore, the parathyroids of wild gray rats show but few differences from those of stock and gentle albinos. Figure 11 is taken from a gray rat. Gray specimens show often a rather definite arrangement of the cells in the form of cords. This arrangement has been noted in the parathyroids of albinos also, especially in those of older animals. It is, therefore, not peculiar to the gray rats but it is more common among them and is especially more often seen in young grays than in young whites. The exact ages of the gray rats are, of course, not known, but they cover a considerable range of size. The specimens included three pregnant rats, which showed no peculiarities of the parathyroid.

Measurements have been made of the glands of all three groups of rats, but do not as yet yield results that we consider significant. A large variation in the relation of the size of the parathyroid to body weight appears to exist in albino rats. Until sufficient material has been accumulated to work out a normal growth curve for the gland it is impossible to come to definite conclusions about its size in different groups of animals.

3. *Other Factors Influencing the Onset of Tetany:* We have investigated several other conditions which have been said to influence the susceptibility of rats and other animals to tetania parathyreopriva. We have not found any structural changes in the parathyroid itself. A number of rats have been fed on meat for a considerable length of time, and their parathyroids were examined at the end of the experiment. The glands proved to be indistinguishable from those of rats fed on the ordinary meat-free diet of the colony. Another group of glands studied were those taken from females with new-born litters. The period of pregnancy and lactation is one in which the rat is peculiarly susceptible to tetany. The glands of nursing females and those taken at various periods of pregnancy do not show differences from those of any other rats. There were twenty of the meat-fed rats, ten of those lactating and seven pregnant females. When no indication of change was seen the line of work was discontinued.

#### DISCUSSION OF EXPERIMENTAL RESULTS

It appears to us from the studies we have made of the parathyroid under various conditions that the reason for the varying susceptibility of the rat to tetania parathyreopriva is not to be found in the histological condition of the gland itself. It may be that there are ultra-microscopic differences in the organ. On the other hand, the susceptibility may depend on the presence or absence of accessory parathyroids or on the ability of the animal to establish a compensatory mechanism in some other organ. The solution of the problem as far as anatomy can offer one may be found not in the histology of the parathyroid but in that of some other organ or organs of the body.

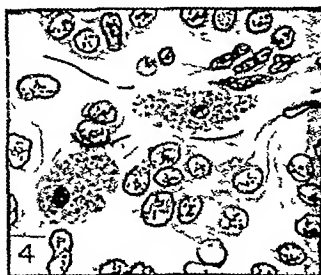
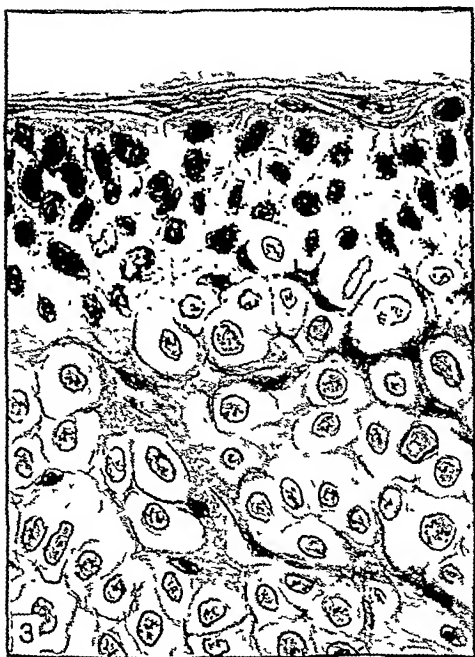
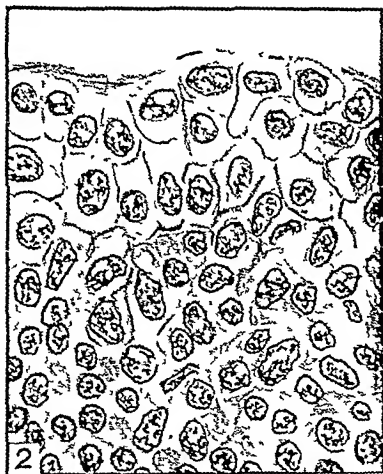
#### SUMMARY

Three types of cells are to be observed in the parathyroids of white rats: chief cells, light cells and chromophiles. The chief cells are the most constant and are undoubtedly the functionally important cells of the gland.

Age changes are slight, consisting in differences in arrangement of cells rather than in varying kinds of cells. Pregnancy, differences in nervous condition, and differences in diet do not

## PLATE 1

- Fig. 1. Chief cells. Albino rat thirty days old.
- Fig. 2. Chief cells and pale cells at the periphery of the gland.
- Fig. 3. Chromophile cells.
- Fig. 4. Eosinophile cells in the connective tissue.
- Fig. 5. Basophile cells in the connective tissue.





## PLATE II

Fig. 6. Chief cells from parathyroid of cat, showing arrangement in a follicle.

Fig. 7. Eosinophiles (Welsh's cells) from the parathyroid of a cat.

Fig. 8. Eosinophiles (Welsh's cells) from human parathyroid.

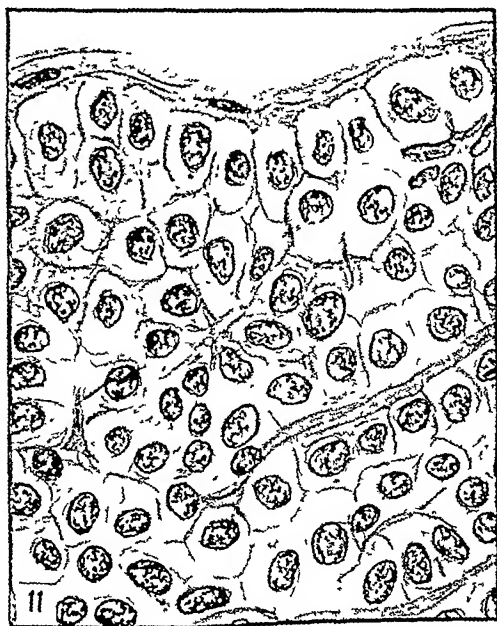
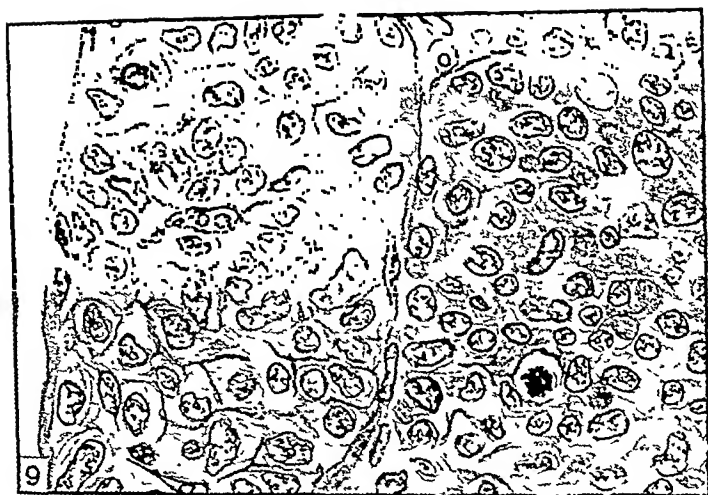


## PLATE III

Fig. 9. Parathyroid of new-born albino rat.

Fig. 10. Parathyroid of albino rat seventy-five days old, showing arrangement of chief cells in cords.

Fig. 11. Parathyroid of gray rat.



produce morphological changes in the parathyroid. The glands of wild gray rats are indistinguishable from those of albinos.

A comparison of the rat material with parathyroids of cats and with human specimens shows that the eosinophiles which have been observed in man are rare in cats and have no counterpart in rats.

I take pleasure in acknowledging my indebtedness to Dr. H. H. Donaldson for his advice and for the material supplied by him. Also to Mr. Chandler of the University of Arkansas, whose assistance has been most valuable.

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# HEMOSIDEROSIS: A CASE OF "BRONZE DIABETES" WITH ENDOCRINE DISTURBANCES (SEXUAL REGRESSION)

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The disorder of metabolism, variously called bronze diabetes, diabète bronzé, hemochromatosis and hemosiderosis, is so infrequently encountered as to be of unusual interest. Howard (1) found only 75 cases in the literature through the year 1918, and since then very few have been added. The case which it is the object of this communication to describe is worthy of note because it presents not only the usual feature of this relatively rare syndrome, but also shows, in sexual regression, evidence of a profound endocrine disturbance.

## REPORT OF CASE

A. Laf, a vagrant laborer 28 years of age, was admitted to the University Hospital August 16, 1922, complaining of excessive thirst and urination, and of weakness. He was born of French parents in the United States. His history was of no medical interest up to the age of 17. Until that time his development was, in his estimation, entirely normal. He believed that there was nothing unusual in his sexual capacity and he stated that he had frequently indulged in coitus. During this year, however, he found himself sexually impotent, and he observed that he did not require shaving as did others of his age. Both these conditions remained unchanged during the ten years previous to his admission to the ward. He had observed no changes in figure or in his genitalia after he was 17 years old.

Five weeks before he came to the hospital, he suffered from an unappeasable thirst, and found that he was urinating frequently and copiously. Associated with these symptoms were progressive weakness, lassitude and loss of weight; no clear record of the latter could be obtained, but he stated that during the previous winter he had weighed 164 lbs., and that his loss to 121 lbs. had occurred almost entirely in the previous five weeks. He was not certain that his skin had ever been any less pigmented than it was at the time of his first examination.

Examination showed a feminine type of figure. The height was 66 inches and weight 107 lbs. The pubic hair was very sparse and of the feminine distribution, with no extension toward the umbilicus. There were a few fine hairs on the face and in the axillae. The skin over the entire body was copper brown, somewhat icteric, resembling the tan resulting from exposure to sunlight. The pigmentation was most intense over the hands, face, neck and arms. The skin of the

backs of the hands was mottled, with small areas 2-3 mm. in diameter in which the pigmentation was much less intense than in the surrounding areas.

The teeth were in very poor condition. The heart was enlarged to percussion, and the cardiac area as determined by orthodiagram was 162% of normal. There were numerous extrasystoles which were shown by electrocardiographic records to be of both auricular and ventricular origin. The liver was enormously enlarged, presenting itself to inspection as a dome-shaped mass between the ensiform cartilage and the umbilicus. The left lobe was especially enlarged. The liver was firm, the edge sharp and the surface nodular. The spleen was palpable. The veins over the abdomen were somewhat more prominent than is usual. The genitalia were of the pre-adolescent type and the testicles were about 1 cm. in long diameter. The neurological examination was negative.

X-ray plates of the region of the pituitary gland revealed no evidence of abnormality. X-ray examination of the gastro-intestinal tract after a barium meal showed no unusual features except rapid emptying of the large bowel. The blood Wassermann was negative. Blood examination showed: hemoglobin, 80%; R. B. C., 4,100,000 per ccm.; W. B. C., 6,500 per ccm.; smear and differential, normal. Blood sugar at admission was 320 mg. per 100 cc. A blood culture gave negative results. The fragility of the red blood cells was normal. The blood pressure was 120 systolic, 80 diastolic. The stools were normal. In the urine 59 gm. glucose was found in the first 24 hour specimen; hemosiderin was demonstrated by the method described by Rous (2); the urine was otherwise negative, including the ferric chloride test. The basal metabolic rate was within the limits of normal variation. An excised specimen of skin was described by Dr. A. S. Warthin as follows:

"With hemalum and eosin staining, the skin shows a brown to yellowish brown pigment distributed nearly uniformly at the level of the basal cells of the epidermis. In the situation it seems to be located in the processes of the connective cells running between the epithelial cells, rather than in the epithelial cells themselves. The amount of pigment corresponds to that found in a very heavy tan or a light mulatto, and with this stain cannot be differentiated from melanin. With alum carmine staining an additional pigmentation can be seen in the form of glistening intracellular granules occurring in the basement membrane of the sweat glands. With the Berlin Blue reaction both of these pigments are found to be iron containing: that around the sweat glands stains a deep bright blue as if composed of hemosiderin alone, while that in the epidermis is of a greenish blue as if from a mixture of hemosiderin with hematoïdin or melanin, probably the latter."

The course of the disease in the hospital was characterized by a very rapid loss of ability to utilize glucose. At first there was no difficulty in keeping his urine free of sugar on diets of the type described by Newburgh and Marsh (3), but within two months this became impossible in spite of extreme reduction on the diet, and efforts to control the glycosuria were abandoned. He died in diabetic coma November 16, 1922, exactly three months after admission to the ward, and only a little more than four months after the onset of active diabetic symptoms. The body was examined nine and one-half hours after death. Following is a summary of the autopsy as reported by Dr. A. S. Warthin, to whom I am grateful for permission for its use.

#### AUTOPSY

*Brain:* The meninges show congestion and edema. In the subarachnoidal space are great numbers of hyaline concentric concretions, some with lime salt deposit. No pigmentation is found in the sections not treated with iron. The meninges are thickened. The ventricular ependyma other than that of the choroid plexus shows no pigment in untreated sections.

The *choroid plexus* shows evidence of chronic passive congestion with acute exacerbation. Numerous brain sand concretions are present. Ependymal layer shows very irregular hemosiderosis. In some areas the cells are packed full of hemosiderin granules. In others, the pigment is barely visible.

The *pineal gland* contains a few sand bodies and shows very slight pigmentation.

*Pituitary*: The anterior lobe shows some patches of increased stroma. There is marked congestion. An excessive number of basophilic cells and an irregular hemosiderosis of the gland cells is seen. In the intermediate lobe there is a fibrosis and the nervous tissue shows no pigmentation.

The *spinal cord* shows post-mortem change but no pigmentation.

*Heart gross features*: The cardiac apex is at the upper border of the fifth rib in the anterior axillary line. The organ weighs 400 grams. It measures  $15 \times 12 \times 4\frac{1}{2}$  cm. The sub-epicardial fat is exceedingly scant in amount. Some serious atrophy is shown. Towards the base there are a few small sub-epicardial hemorrhages. The apex is formed jointly by both ventricles, the right ventricle seeming to be proportionately larger than the left. Near the apex, on the surface of the left ventricle there is a small soldier's spot.

Of the *right heart*, the ventricular wall is 4 mm. in thickness. It is very pale, apparently from a deep fatty infiltration, but the fat is nearly devoid of lipoid substance. Of the *left heart*, the ventricular wall averages 14 mm. in thickness. The cavity of the left ventricle is somewhat globular in outline, as from moderate dilatation, without muscular hypertrophy. No fibroid patches are visible to the naked eye. All portions of the myocardium show a definite yellowish-brown color, more marked than that usually seen in brown atrophy and probably due to hemochromatosis.

*Microscopic examination* shows marked fibrosis which is very diffuse and most marked toward the endocardium with individual heart muscle fibres, many of which show marked hypertrophy and others atrophy. The majority of the fibers contain hemosiderin, irregularly arranged within the cell, but not showing the arrangement of hemofuscin. Frequently peri-nuclear, in some cases it is at one pole of the fibre, away from the nucleus, while in other cases it is diffuse throughout the cells. In more atrophic fibers the pigment is concentrated and appears darker. In the stroma there are numerous pigmented fibroblasts and endothelial cells. The pigmentation of the heart muscle is most marked in the fibroid areas nearest the endocardium.

The *aorta* shows very slight sclerosis with no pigmentation apparent in the untreated sections.

The *lungs* show the characteristics of chronic passive congestion with acute exacerbation and edema. Occasional pigment-containing cells are seen in the alveoli, the pigment being hemosiderin. The bronchial nodes are atrophic and show moderate anthracosis, but relatively little hemosiderin. The larger bronchi show a severe chronic catarrhal bronchitis with striking hemosiderosis of the mucous glands, many cells of which are packed with hemosiderin granules. One lung shows a chronic thickening of the pleura. Frozen sections show marked lipemia with fatty embolism.

The *tonsils* are atrophic with marked bone and cartilage. The neighboring mucous glands show hemosiderosis of the cells.

In the *larynx* and *pharynx* all mucous glands show marked hemosiderosis.

The *thymus* is persistent and hyperplastic with great numbers of corpuscles of Hassal present in various stages of concretion forma-



tion; many are calcareous. Numerous pigmented cells are seen in the stroma.

The *thyroid* colloid is somewhat increased. In the larger follicles it shows a peculiar granulation and conglomerate formation with some lime salt deposit. The cells lining the acini show more or less hemosiderosis. In the iron reaction preparation the hemosiderosis is found to be very irregularly distributed.

*Spleen* gross features: The organ weighs 320 grams. It measures 17x11x4 cm. It is nearly free, except a very few small adhesions to the omentum about the hilus. Upon bleeding out it becomes somewhat smaller with moderate wrinkling of the capsule. Externally there are no gross changes evident. On section the splenic pulp is a rather pale reddish-purple with only moderate congestion. It does not show hemosiderosis to the naked eye. No lymphoid hyperplasia and no increase in stroma are seen.

*Microscopic* examination shows marked lymphoid atrophy, diffuse fibrosis and sclerosis of vessels. The amount of hemosiderosis, while greater than that of the normal spleen, does not in any way compare with the hemosiderosis of the lymph nodes.

The *large intestine* shows marked chronic catarrh but no pigmentation of the mucoid cells.

The *appendix* shows post-mortem change in the mucosa. No pigmentation of the wall is found.

The *small intestine* shows chronic catarrh with pigmented epithelial cells toward the base of the glands and in the stroma, with slight hemosiderosis.

The *stomach* shows slight chronic catarrh. Both chief and parietal cells show marked hemosiderosis, while the mucous cells of the upper layer show practically none.

*Pancreas* gross features: The organ is of about normal size but definitely softer than normal. On section the peri-pancreatic fat is found to be scant in amount and quite edematous and shows a very large number of small, pinhead-sized areas of fat necrosis. The pancreatic substance is deep purplish, reddish-brown in color, appearing almost hemorrhagic. The lobules are less distinct than normal, although there are coarse bands of stroma and stripes of fat necrosis over the cut surface.

*Microscopic* examination shows complete post-mortem digestion and marked atrophy of the lobules. In the body and toward the tail there is marked fatty atrophy. Increase of stroma with inflammatory infiltration is present; also marked chronic pancreatitis. The cells of the atrophic acini contain hemosiderin in about the same degree as the liver cells. The pancreatic ducts are dilated, many of them with thickened walls, and there is a new formation of ducts and acini. Hemosiderin is also found in the cells of these new-forming ducts. Only a few islands of Langerhans can be found. These seem small and show a hemosiderosis of their cells. No fibroid islands are found. In the peri-pancreatic fat tissue there are areas of inflammatory infiltration.

*Liver* gross features: The weight is 3130 grams. It measures 32x27x7½ cm. The surface is very irregular, being cut into several anomalous lobules by deep fissures, and shows also depressed areas which are firm, starlike, and show radiating fissures. In these respects the liver suggests a *hepar lobatum*. There is a marked general increase of stroma which is appreciable by palpation of all portions of the liver. The surface is uniformly coarsely granular upon palpation. Through the capsule, the lobules show distinctly, as cut

off by interlobular increase in connective tissue. The color is definitely brown. The cut surface shows a moderate congestion and a very marked increase of stroma which is interlobular in its distribution. The liver cells show a marked yellowish-brown color as if from hemochromatosis.

*Microscopically* the liver presents the picture of an interlobular or atrophic cirrhosis. There is no intralobular increase of connective tissue. The interlobular connective tissue is quite hyaline in character and not very cellular; it shows but little inflammatory infiltration, but does present a marked hyperplasia and regeneration of small bile ducts and liver cell cords. A majority of the lobules are small. The liver cord arrangement is very indistinct and the intralobular capillaries are collapsed. The liver cells vary in size and show marked atrophy, cloudy swelling and occasional fat droplets. Practically every liver cell shows a granular brown pigment which gives the iron reaction of hemosiderin. This pigment is somewhat irregularly distributed throughout the lobule, but in general is more abundant in the peripheral zone. It is still more abundant in the atypical, newly formed liver cords and small bile ducts of the interlobular connective tissue. In these, the pigment is more coarsely granular and clumped into heavier masses. It appears also in some endothelial and connective tissue cells of the stroma, but is more marked in the epithelial cells. In the iron reaction sections no other pigment but hemosiderin is visible. All the pigment within the liver appears to be iron containing. Throughout the liver lobule, the star cells of Kupffer appear especially loaded with hemosiderin. Occasional lobules show groups of liver cells in which there is very little iron pigment within the liver cells, while the endothelial cells show a greater degree of hemosiderosis. In the liver cell the hemosiderin occurs particularly in a zone immediately around the nucleus or situated at one side of the nucleus. Some nuclei show hemosiderin granules within the nucleus itself. In the post-mortem clots in the blood vessels, the fibrin threads give an especially bright blue iron reaction, quite different in color tone from the more greenish-blue granules in the liver cells. The yellow elastic tissue of some of the blood vessels also gives a bright blue iron reaction. Localized hyaline thickenings of the capsule without pigmentation is seen.

The *gall bladder* shows chronic catarrhal cholecystitis with slight induration of the wall.

The *adrenals* in the gross show a rather abundant fatty capsule with the fat showing marked edema and some serious atrophy. The adrenal substance shows a marked atrophy of hypoplasia affecting both cortex and medulla. The medulla is deep brownish in color. The cortex is a pale yellow without definite patches of lipoidosis.

*Microscopically* the adrenals show atrophy; chronic passive congestion; marked hemosiderosis of the glomerular zone and slight of the fascicular zone, diminishing toward the reticular. Around the central vein are groups of heavily pigmented cells, apparently endothelial. Inflammatory infiltrations extend throughout the reticular zone and medulla. In the iron reaction stains the preponderance of the hemosiderin in the glomerular zone is very striking.

*Kidneys* gross features: The scant fatty capsule shows some serious atrophy. The fibrous capsule strips readily, leaving a surface which is practically smooth and is pale except for a few dilated stellate veins. On section there is found a moderate general passive congestion and moderate cloudy swelling of the cortex which rises slightly above the medulla. The color is practically normal with a very faint, scarcely perceptible yellowish tint. The left kidney weighs 235 grams.

and measures 15x7x4 cm.; the right weighs 215 grams and measures 13x7x4 cm.

*Microscopic* examination shows atrophy, cloudy swelling and groups of lipoid cells in the convoluted tubules. No glycogen deposits are found, but numerous hyaline casts. Fibrosis of the basement membrane of the pelvis and healed pyelitis are seen. In sections not treated with the iron reaction very few tubules show any pigmentation and these are chiefly in the medullary portion. The iron reaction shows the hemosiderosis of the kidney to be most marked in the loops of Henle, both ascending and descending limbs and in the corvex in the straight tubules away from the glomeruli. The convoluted tubules show very little and only an occasional glomerulus shows any.

The *urinary bladder* gives negative findings with no pigmentation in the non-iron stained sections.

The *retroperitoneal lymph nodes* show chronic lymphadenitis, congestion and edema with hyaline change and varying degrees of hemosiderosis. The hemosiderosis is found particularly in the endothelial cells of the sinuses. Some nodes are heavily packed with pigment while others show relatively little. The *retroperitoneal hemolymph nodes* show a marked degree of hemosiderosis in the endothelial cells of the sinuses and great numbers of pigmented hemophages. The lymphoid tissue of other lymph nodes is atrophic. The sinuses show marked proliferation of the endothelial cells and marked sinus catarrh, with varying degrees of hemosiderosis of the endothelial cells.

The *testes* are both present in scrotum and are very small. On section both show a complete fibroid atrophy, the fibrous tissue being somewhat edematous, giving it a slightly gelatinous consistency. No normal seminiferous tubules can be seen.

*Microscopically* complete aspermatogenesis is evident with the germinal cells reduced to a single layer showing marked vacuolation or completely absent. The basement membrane shows marked hyaline thickening and there is a diffuse increase of hyaline stroma but no active inflammation. The interstitial cells are greatly reduced with marked atrophy. The blood vessels show marked sclerosis. The atrophic interstitial cells show but little pigment, but many of the atrophic tubules show hemosiderosis in the living cells.

The *prostate* is very small, like that of a boy preceding puberty. *Microscopically* it appears atrophic with very small glands. The ducts show slight chronic inflammation. Scattered glands show hemosiderosis of the epithelium.

The *skin* shows slight melanosis of the rete of a degree about like that of a light brunette. Throughout the corium and subcutaneous tissue there are numerous large cells in the connective tissue, apparently lymphatic endothelial cells, packed with hemosiderin. The cells of the sweat and sebaceous glands do not show the hemosiderin, but the endothelium of the lymphatics around the gland shows the pigment.

The *final pathological diagnosis* is: Atrophic cirrhosis with generalized hemosiderosis and chronic atrophic pancreatitis; terminal lipaemia (bronzed diabetes); hemosiderosis of liver, pancreas adrenals, retroperitoneal lymph nodes and hemolymph nodes, testes, kidneys, spleen, thymus, thyroid, myocardium, choroid plexus, hypophysis and mucous glands of upper respiratory tract; persistent thymus; hypoplasia of adrenals; fibrosis of testes; eunuchoidism; general endocrinopathy; atrophy and passive congestion of all organs; old tubercles in ileo-cecal and mesenteric lymph nodes.

## DISCUSSION

This patient presented two distinct syndromes, bronze diabetes and eunuchoidism. Several points should be emphasized in regard to each.

The clinical course and pathological findings were entirely characteristic of pigment cirrhosis with diabetes. It is interesting to note that none of the factors that have been suggested as etiological was found. Special attention was paid to the possibility of chronic copper poisoning, as suggested by Mallory, Parker and Nye (4), but no history was obtained of any source of this metal. The patient was a male, as has been true in nearly all the cases in the literature, but he was somewhat younger than the majority have been, the ages of greatest frequency being between 40 and 60 years. The course from the onset symptoms to death, 41½ months later, is striking and the downward progress as evidenced by failing carbohydrate tolerance was remarkably rapid.

The visceral abnormalities, as determined by both clinical and anatomical examinations, were largely in accord with previous descriptions of this syndrome. The enlargement of the liver, especially of the left lobe, with cirrhosis, the sclerosis of the pancreas, and the widespread pigmentation are characteristic. Myocardial degeneration has been described by the pathologists, but this is the first case in which the cardiac condition was sufficiently serious to attract attention ante mortem. The heart was shown to be enlarged by percussion, and the orthodiagram with Van Zwaluwenberg's (5) method of mensuration showed an increase of more than 50% over normal size.

The pigmentation was remarkable because of the fact that only one pigment could be demonstrated and because of the large variety of tissues in which it was found.

It is ordinarily stated that one of the characteristics of bronze diabetes is the presence of hemosiderin, a pigment giving an iron reaction, and hemofucsin, giving no iron reaction. Sprunt (6) has pointed out that with the more modern methods of staining a larger proportion of the pigment was found to be hemosiderin than was found by the earlier observers. In the case here described the pathologists found no pigment other than hemosiderin. Even in the liver Dr. Warthin states "no other

pigment than hemosiderin is visible. All the pigment in the liver seems to be iron containing." For this reason the term hemosiderosis is applied to this case rather than the more usual hemochromatosis. It is to be noted that in every other way the history and examinations of this patient are in agreement with the classical cases of bronze diabetes.

The distribution of the pigment is of interest, and may be summarized as follows: A high grade of pigmentation was found in the choroid plexus, anterior lobe of the pituitary, heart, mucous glands of the bronchi, pharynx and larynx, thymus, chief and parietal cells of the stomach, adrenals, kidney, retroperitoneal hemolymph nodes, testes and skin. There was a moderate pigment deposit in the thyroid, and little pigment in the pineal, lung alveoli, spleen, intestine and prostate. None was found in the brain, intermediate and posterior lobes of the pituitary, spinal cord, aorta, large intestine, appendix, mucous cells of the stomach and urinary bladder. The degree of pigment in the lymph glands varied widely.

The etiology of the sexual regression is a subject for speculation. Were the two syndromes merely coincident in this patient? Was the sexual regression of pituitary, testicular or pancreatic origin? Is this an example of a pluriglandular disturbance? These interesting questions cannot be answered from the data at hand.

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# THE METABOLISM OF GALACTOSE

## II. BLOOD SUGAR CURVES

### CONTRIBUTIONS FROM THE EVANS MEMORIAL

No. 66, Series A-28

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#### 1. INTRODUCTION

In a recent paper (29) the senior author discussed the results obtained in a study of the assimilation limit for galactose, using normal men and women as subjects. This earlier report, as well as the present article, are portions of a comprehensive study undertaken to establish, if possible, a series of objective criteria for the diagnosis of disturbed endocrine functions. In the present paper no direct reference will be made to the diagnostic phase of the work. Cases are collected into groups of etiological relationship solely for convenience and to determine a basis of equality in comparison. In beginning these studies, nearly 10 years ago, the choice of a sugar as the basis for one part of the work was of paramount importance.

As a sugar not foreign to the human economy; with a low assimilation limit; of so simple a structure as to be capable apparently of direct assimilation, and susceptible of preparation in a state of high purity, galactose presented itself as the sub-

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\* Presented before the American Chemical Society, Division of Biological Chemistry, New Haven, April 6, 1923.

stance of election. The basis for these statements is discussed in greater detail in the article already cited.

The present paper deals with the effects upon blood sugar levels, produced by feeding doses of this sugar under carefully controlled and strictly comparable conditions. As the terms, "tolerance threshold," and "assimilation limit," are used today somewhat indiscriminately to designate, on the one hand, a provocative melituria or "glycuresis," and, on the other, a glycemia superior to that at which the so-called renal threshold is controllingly operative, the concepts implied in these several terms may be analyzed.

## 2. THE THRESHOLD OF TOLERANCE

Initially, the term, "tolerance threshold," or better, "assimilation limit," was used to designate that quantity of a given carbohydrate which, on administration, would produce a transitory but demonstrable melituria in an individual otherwise sugar free. The criteria for a positive test ranged from the appearance of a mere trace to the elimination of not less than several grams. The criterion once established, however, the test was equally applicable to the diabetic rendered sugar free by careful dietary regulation, the subject whose capacity for carbohydrate utilization was modified by other causes, and the so-called normal individual.

The improvement of the methods of analysis of blood, with the elaboration of technique of other methods of administration than by the oral route, and through these means, the rendering concrete of the concept of the so-called renal threshold in relation to the sugar level in the blood—all have tended to make the term less definitive in its significance. In short, in using the term today it is essential straitly to indicate the limiting conditions and form of administration together with the channel of ingress, to establish criteria for positive and negative findings, and to determine the basis for the comparison whereby departure from normality may be demonstrated.

Broadly speaking, the field may be divided into two major groups: that in which the end result of an induced and transitory melituria only is considered, and that in which the melituria is incidental to an increase in blood sugar level above the so-

called renal threshold or in which the rise in blood sugar is the sole criterion, the possible melituria being ignored. Glycosuria without hyperglycaemia, as in the so-called renal diabetes (the later word a misnomer), and hyperglycaemia without glycosuria, as in many cases of true diabetes, represent the extremes of the second group. The present discussion will be confined in the main to this second class, the threshold as determined by melituria being considered only as it is incidental to the other. Liefman and Stern (22) have applied the terms "internal tolerance" to the capacity of the tissues to utilize sugar, and "external tolerance" to indicate changes in kidney permeability.

In the earlier article it was demonstrated that for each individual there was a definite dosage of galactose, which, administered orally in 10 percent to 20 percent aqueous solution, with the subject in a basal condition, would produce a transitory melituria detectable by a sensitive copper reduction test (Benedict's), and that a dose of 10 grams less under similar conditions would fail to produce this result. Further, that for the so-called normal male 30 grams and for the female 40 grams was the dosage producing positive response. In all subsequent discussion the convention will be adopted of designating as "super-tolerance" those doses which produce detectable melituria, and as "sub-tolerance" those which fail to do so. To avoid confusion, it should be noted further that the amounts given above for normal individuals do not hold in the cases about to be discussed, the individual tolerance in this conventional sense being a personal characteristic and determined independently for each subject as such.

### 3. BLOOD SAMPLES

As the majority of the subjects studied were patients in the hospital, the means to be adopted for obtaining blood samples was a factor in the problem. Theoretically, blood taken directly from the vein should give a more representative index of the momentary blood sugar level than that obtained by other methods. The emotional element cannot be ignored, and this operates, on the one hand, directly on the sugar level, and on the other, and equally potently, indirectly on the quality of cooperation of the subject. The possibility of contamination of



blood taken otherwise than directly from the vein led to a brief preliminary study.

(These measurements were performed some twelve months prior to the appearance of the excellent and comprehensive study by Foster (12a), certain details of which will be discussed elsewhere in this paper.)

A few brief observations showed that the use of the ear as a site for drawing blood involved less discomfort than that of the finger, hence all measurements were confined to the former. As the quantity thus obtainable was small, the amounts of the ear blood samples were determined by weighing and a mean specific gravity of 1.060 was assumed. The venous blood was procured by the usual technique, the cubital veins being the site of election.\*

The Folin-Wu (13d) methods of blood analysis were followed throughout. The results of this brief preliminary study are given in Table I.

TABLE I  
Comparison of Ear and Vein Blood Sugar

Subject Sex		A		
		I F	II M	III M
Ear .....		105	112	125
Vein .....		85	107	111
Ear / Vein %—100%...		+ 23%	+ 5%	+ 13%

		B					
Subject	Sex	Galactose		Site	Blood Sugar		
		Dose	Excre.		—15 m.	+45 m.	+120 m.
I	F	20	0	Ear .....	100	124	106
				Vein .....	84	112	99
				Ear / Vein..	+ 19%	+ 11%	+ 7%
II	M	40	+	Ear .....	110	182	112
				Vein .....	100	175	95
				Ear / Vein..	+ 10%	+ 4%	+ 18%
IV	M	20	0	Ear .....	...	138	97
				Vein .....	...	132	92
				Ear / Vein..	...	+ 5%	+ 5%

It is evident from the few figures here given that the results of the analyses of ear blood show no fixed relationship to those of venous blood. To avoid this element of uncertainty, all subsequent blood samples were taken by venipuncture.

\* It is with great pleasure that the authors acknowledge their indebtedness to the friendly co-operation of Drs. S. B. Hooker and J. B. Vance, by whom were performed all of the vein punctures connected with this work. Any emotional factor was eliminated by their most skillful technique.

#### 4. COMPARISON OF GALACTOSE WITH GLUCOSE STANDARD

Another point requiring investigation was the reaction of galactose to the reagent. Bertrand (7), among others, has shown that galactose has a lower reducing rate than glucose. Further, by the procedure used, the time element is a potential factor. To answer this question, solutions of glucose, galactose, and percentage mixtures of the two were prepared by weighing, and the apparent and real content compared. The results are given in Table II.

TABLE II  
Time of Boiling

Composition mgm per 100cc		6'		6' 12'		12' 12'		Standard Test Solution
Glu.	Gal.	Obs.	Cal.	Obs.	Cal.	Obs.	Cal.	
100	0	100	..	105	..	100	..	
75	25	94	94	102	101	..	96	
50	50	88	89	97	97	..	93	
25	75	83	83	91	92	..	89	
0	100	77	..	88	..	85	..	

From the above it is obvious that, as the blood, after the administration of a test meal, contains both glucose and galactose, the results obtained by analysis will always be less than the truth. In many instances this may well exceed 10 percent. Blood sugar curves produced by feeding galactose are, at best, but approximations, the true shape of the curve being more pronounced than that observed.

#### 5. METHODS

*a. Schedule.* As was previously stated, the present report constitutes but one phase of a more comprehensive study on functional abnormalities of the endocrine system. The subjects, whether normal controls or patients, were admitted to the hospital for a period of not less than seven days. During the entire period of stay, they followed an elaborate and carefully designed schedule, the object of which was to secure a definite uniformity of conditions and thus insure comparable results. The full schedule need not be reported here; it is only necessary to state that the first four days of residence were devoted to the establishment of a nutritional equilibrium and a thorough testing of certain of the contributory functional capacities of the liver, kidneys, etc.

On the morning of the 5th day the following schedule was begun (Table III).

TABLE III

<i>Day 5.</i>	5:00 A. M.	Empty bladder and discard. Begin collection of 1st urine.
	6:45 A. M.	Blood No. 1 taken.
	7:00 A. M.	Complete collection of 1st urine. Start collection of 2nd urine. Test meal of galactose.* I, 30 gms. for men, 40 gms. for women, +15 gms. urea dis- solved in 200-300 c.c. water.
	7:45 A. M.	Blood No. 2 taken.
	9:00 A. M.	Complete collection of 2nd urine. Start collection of 3rd urine. Blood No. 3 taken.
	11:00 A. M.	Complete collection of 3rd urine. Start collection of 4th urine.
	11:05 A. M.	Breakfast. Patient arises.
	1:00 P. M.	Complete collection of 4th urine. Start collection of 5th urine.
	3:00 P. M.	Complete collection of 5th urine.
<i>Day 6.</i>		Repeat Day 5, using dose I $\pm$ 10 grams galactose and no urea. Only Urines 2, 3 and 4 are collected. Continue daily tests until + and 0 limits are established.

*b. Diet.* During the entire period of study the subject followed a specific dietary regimen. It is obviously desirable that no partial carbohydrate inanition shall exist,<sup>†</sup> and equally, it is felt, an adequate amount of protein in absorbable form, should be ingested. Diets were designed to contain not less than 6 grams of carbohydrate and 1.66 grams of protein per kilogram of body weight. Fats were added in suitable amount to determine a gross energy intake of not less than 45 calories per kilo.

Another point upon which emphasis was laid was to render the diet as varied and palatable as possible. For studies of

\* It should be stated that only galactose of the highest obtainable grade has been used, and its purity thoroughly tested. The earlier material was derived from a variety of sources, all of the later work, including the present report, with the purest grade of Pfanstiehl galactose.

<sup>†</sup> Traugot (32), using glucose in oral doses of varying amount, has emphasized the necessity of carbohydrate saturation in the performance of all tolerance threshold tests.

this character, exact evaluations of the several constituents is unnecessary and computations based upon Locke's compilation (23) were sufficiently accurate. On the other hand with studies of the duration of a week or more, the mental factor is not negligible, particularly with a group of individuals who are not in normal health and who lack, in large measure, the urge of scientific interest and the enthusiasm of dietary propagandists.

In certain cases, however, where dietary regulation had been followed for a number of years, the prescribed schedule was modified in accordance with the practice of the individual. Further, a few of the subjects had allergic idiosyncracies which entailed yet other modification.

The writers feel that due regard to preliminary nutrition is an essential in the standardization of these tests.

*c. Analytical Procedures.* All blood analyses were made by the Folin-Wu (13d) procedures, the urea nitrogen being aerated and not distilled. No correction was made for blood ammonia.\*

Filtrates were prepared immediately upon drawing the blood and analyses performed inside of three hours. Urine sugars were determined by the Benedict (6a) methods, while urine urea was estimated by the Folin urease method (11a), and the corrective ammonia factor by the micro-method of the same author and Macallum (11c).

That the reducing body found in the urine was galactose was somewhat taken for granted. The earlier work by Bauer (4a, b) and his successors† with the mucic acid test would seem to be definitive. The present authors have tested a large number of positive urines with the Tollens test (Phloroglucinol-Hydrochloric Acid) with uniformly affirmative response. In addition, a number of osazones have been formed in positive urines, the crystal form of which under the microscope has been identical with that of similar osazones prepared from control urines to which galactose had been added. Isolation and determination of the melting point have not been done.‡

\* That the ammonia content of the blood cannot be a source of error of disturbing magnitude has been shown most conclusively by Benedict and Nash (6b), and has recently been confirmed by Russell (30), in studies on nephritics.

† See also Hirose (16), and Wagner (33). The latter found that his galactose yielded 72 per cent of mucic acid and that the sugar in the urine gave a yield of mucic acid 70 per cent of the titration value calculated as hexose. Basedowians and neurotics formed an exception to the above, and he records one Basedowian in whose case after a galactose test meal, all sugar in the urine was apparently glucose.

‡ No further question of this point would have been raised but for the appearance of an article by Bodansky (8), in which the author states that after the administration of heroic doses of galactose with the production of a marked melituria, little or no galactose was to be found in the urine. The fact that Bodansky used dogs for his subjects may offer an explanation of the discrepancy.

Reiss and Jehn (28) also verified galactose by the osazone. That some of the reducing material in the urine is galactose must be regarded as established.

## 6. RESULTS

*a. Blood and Urine Urea.* A number of writers on this topic have ascribed the heightened assimilation limits observed in certain disturbed endocrine states to a lessened rate of absorption of the sugar from the intestine. The improved principle of tolerance testing proposed by Beeler, Bryan, Cathcart and Fitz (5) was designed to throw light on this as on other questionable factors. The results, however, are not sharply conclusive. In the human subject only indirect methods seem available if the oral route be adopted. In the present study, to secure information on this point, the simultaneous administration of urea with the galactose test meal was adopted for three reasons. First, the determination of a series of blood ureas should give some index of the absorptive power of the intestine. Second, the mild diuretic action of the urea might be beneficial. Third, the provocative ureaemia (Pirondini [27]) would give supplementary evidence concerning the integrity of kidney function. The results obtained are summarized in Table IV.

TABLE IV

Diagnosis	No. of Cases	Blood Mgm. per 100 cc. % increase				Urine Total grams % increase		
		-15'	+45'	+120'		5-7	7-9	9-11
Gonad .....	8	12.2	25.9	25.7	1.23	4.33	3.90	2.90
			112	111		254	217	136
Thyroid .....	7	15.2	26.7	25.8	1.64	2.90	3.33	3.06
			76	70		77	103	86
Pituitary (dys.) ...	4	14.7	24.6	25.7	1.87	4.35	3.40	2.39
			67	75		133	82	28
Pituitary (hypo.) ..	6	12.8	18.2	24.2	1.91	3.57	3.12	2.75
			42	89		87	63	44
Pluriglandular (Pit. prim.) .....	3	12.6	19.7	23.7	1.29	1.92	2.55	2.59
			56	88		49	98	101
Pluriglandular (miss.) .....	5	14.3	26.2	27.9	1.54	4.14	3.20	3.00
			83	95		169	108	95

In general it may be said that, from the blood urea curve,

two of the groups does there seem to be any evidence of delayed absorption, and these exceptions have all reached a significantly high level inside of the two hour period. Greater irregularities are evident in the urine urea sequences, but here

again only one fails to show a point of downward inflexion in either the second or third period following the meal, and that, too, in spite of the fact that breakfast entered as a disturbing factor in the 11 to 1 collection.

Economy of space forbids the tabulation of the data of the individual curves in this paper. It may be said, however, that they give evidence that while there is a general tendency for high blood levels to parallel increased elimination, there are too many exceptions noted to warrant the assumption of a direct relationship. One is constrained to regard blood and urine levels as related but not mutually interdependent phenomena.

*6b. Blood Sugar. Super-tolerance Dose.* As was stated earlier in this paper, it has recently been shown that for each individual there exists a definite dosage of galactose which, when administered under specifically defined conditions, will produce a transitory but detectable melituria. Likewise, a dose of 10 grams less in amount, will produce only negative results.

Further, this conventionally termed threshold is at 30 grams with normal male adults and 40 grams with females. In a variety of pathological conditions, this assimilation limit changes—in some it is notably raised, in others lowered. As will be shown later, the relationship of the dose administered to this so-called tolerance threshold of a given individual, determines in largest measure the type of blood sugar curve elicited by experiment. For this reason, the results obtained are collected and tabulated under the several captions of Super- and Sub-tolerance Doses, following the convention earlier adopted. The results obtained with a few normal individuals and with subjects illustrating a variety of endocrine conditions, to whom doses producing a transitory melituria had been administered, are collected in Table V. It may be said, in passing, that the diagnostic significance of these data is omitted from the present paper. For convenience's sake, however, as in the discussion of the urea curves, the cases are grouped according to an etiological relationship.

The group of four normals present a relationship shown to be typical in this study. Three give substantially so-called normal curves, while the fourth shows a slight fall at the end of forty-five minutes, and recovers to a higher level than the

weight being attached to curve form. Further, had the real maxima been ascertained in each case, the curves plotted probably would have been even more of a medley than is the case.

The complete independence of observed hyperglycaemia and melituria is strikingly illustrated, and this with due recognition of the fact that the flatter curves show maxima which fall short of the truth.

*6c. Sub-tolerance Doses.* Comparison with the curves obtained with sub-tolerance doses is interesting. These data are collected in Table VI.

Case No.	Physical			Group	Tolerance		Blood Sugar Curve					Remarks
	Age yrs.	Sex	Weight kg.		+	0	Dose gm.	Elim. gm.	Time			
									-15'	+15'	+120'	
A-18	28	M	74.3	N	30	20	20	0	85	83	78	Slow absorption Basal Met. -41%.
19	24	M	71.6	N	30	20	20	0	78	77	76	
B-38	25	M	58.0	N	30	20	20	0	69	75	74	
B-12	15	M	59.0	A-	30	20	20	0	104	134	111	
62	46	F	48.2	A-	50	40	40	0	76	88	—	
B-13	61	M	60.5	T-	60	50	50	0	75	89	109	
26	24	M	70.5	T-	50	30	30	0	105	95	107	
35	41	F	69.2	T-	50	40	40	0	69	65	76	
36	28	F	114.8	T-	50	40	40	0	73	114	79	
44	41	F	47.8	T-	40	30	30	0	87	109	92	
B-25	26	M	83.2	P-	50	30	30	0	80	94	94	
27	26	M	46.6	P+	13	10	10	0	82	98	84	
28	27	M	86.5	P-	50	40	40	0	89	92	79	
45	34	F	85.7	P-	60	50	50	0	87	96	90	
							40	0	89	100	92	
48	55	F	51.9	P+	40	30	30	0	94	105	95	
51	52	M	80.0	P-	70	50	50	0	88	116	101	
							30	0	90	111	107	
57	23	F	52.9	P-	50	40	40	0	100	96	89	
60	42	M	76.9	P-	50	40	40	0	87	87	88	
							30	0	89	120	92	
65	19	M	53.2	P+	30	20	20	0	83	106	88	
B-40	25	F	44.9	G-	30	20	20	0	86	152	86	
42	34	M	52.9	G-	30	20	20	0	85	98	89	
B-30	45	M	61.3	Pl. G. -	30	20	20	0	75	80	75	
							10	0	71	71	71	
58	34	F	101.6	Pl. G. +	60	50	50	0	86	100	95	
							40	0	90	105	92	
B-66	28	F	77.6	Unclass.	40	30	30	0	87	129	97	

Divergences from the so-called normal curve are here more frequent. The same underlying independence of urine elimination and blood sugar level is here equally manifest. Selecting the same etiological group, the results obtained are graphically shown in Curve II. The pleasing variety observed

strengthens the opinion expressed concerning the super-tolerance doses.

Comparison with two sets of curves in a most comprehensive and careful study recently published by Olmsted and Gay (26) is instructive. The first set (Fig. 3) is labeled "Curves of Hyperthyroidism," and correspond to those of the present author's shown in Curve I. The second set (Fig. 4) are designated as those of hypothyroidism, and correspond to those shown in Curve II of this article. The explanation is patently that with the lowered tolerance of hyperthyroidism, the Janney meal (18a) of 1.75 grams per kilo of body weight was in the majority, if not all of the cases, a super-tolerance dose. The hyperthyroid curves of Denis, Aub and Minot (10) are similar. Similarly, the hypothyroid cases with increased assimilation limits approximate the sub-tolerance dosage.

Certain striking anomalies present themselves on analysis of the complete data. Selecting the results with cases B-30 and 60, the following interesting facts may be noted. With the former (B-30) the observed maximum is apparently in direct relationship to the size of the ingested dose. With B-60, however, the exact reverse is the case, a super-dose of 50 grams producing an "inverted curve," while a sub-dose of 40 produces apparently no change, and the smaller meal of 30 grams gives a characteristic so-called normal curve, with over 30 per cent increase at the maximum observed point. This latter anomaly, i. e., a larger apparent change in blood sugar level with the smaller exciting dose, repeats itself in several of the other cases. See B-39, 47, 49, 61. This anomaly was observed earlier by Leire (21).

Recognizing the individual variations, the average curves are of certain interest. While there is not an exact parity of numbers in the several etiological groups, there are enough observations recorded in the majority to give a rough approximation of the general curve. The summations are given in Table VII.

TABLE VII—AVERAGES

Group	No.	Super-tolerance Dose			No.	Sub-tolerance Dose		
		-15'	+45'	+120'		-15'	+45'	+120'
N. ....	4	79	95	83	3	77	78	76
Pl. G. ....	3	82	102	84	4	81	89	83
T. ....	14	83	113	95	5	82	94	93
P. ....	15	89	122	96	12	88	102	92
G. ....	17	88	136	99	2	..	..	..

Such differences as occur are hardly intrinsic. Again, barring the normals, the super-tolerance curves approximate the so-called normal, and the sub-tolerance curves are only less pronounced in shape. With these latter it is easy to see how relatively slight variations in the time factor could produce the "inverted curve." They



serve only to reinforce the conclusions already reached. But before drawing final conclusions, it would perhaps be well to consider the results obtained by other investigators, and then to see how far the questions raised by them find possible answer in the present study.

One point only may be emphasized, i. e., that the shape of the blood sugar curve with galactose is implicitly dependent upon the relationship of the amount of the exciting dose to the tolerance threshold of the subject.

## 7. GENERAL DISCUSSION

As was previously stated, all of the earlier literature on the threshold of tolerance for carbohydrates approaches the problem from the standpoint of a provocative melituria, and various quantitative criteria were established for the threshold evaluation. With the development of reasonably accurate methods of blood sugar analysis, the consideration of the hyperglycemia and its influence upon melituria has, in large measure, usurped the field of general interest. With the original concept of a renal threshold rendered concrete by Jacobsen (17) and supported by several later investigators, the level of hyperglycemia has taken on both added interest and greater significance. The highly important research of Benedict, Osterberg and Newwirth (6c), adding the term "glucuresis" to scientific nomenclature, has cast grave doubt on the existence of such a barrier, but the diversity of conditions under which later experimental investigations have been conducted, leaves the question of absolute existence still a moot point.

A variety of sugars has been used, a diversity of methods of administration adopted, and a wide variety of conclusions drawn from the experimental data. Among the possible permutations have been test meals given fasting, with food or after food, fixed doses, progressive doses, and doses graded in relation to body weight, oral and intravenous routes, and samples taken at long or short intervals—to name only a few among the many. In a comparatively recent paper, MacLeod (24), has given an excellent critical review of the more important literature. As several most valuable contributions have appeared since then, however, and as certain points not touched upon in the earlier summary have since assumed significance, a brief recapitulation may be made.

By far the greater number of studies in man deal with the oral administration of a glucose test meal. Two broad subdivisions are possible, namely, those in which a fixed dose has been administered to all subjects, and those in which, following the suggestion of Janney and Isaacson (18b), a dose of 1.75 grams per kilo of body weight is given. In the present study, the continuous intravenous method introduced by Woodyatt

and his co-workers (34), and the few investigations based upon it, have not been taken into consideration. The different conceptual relation introduced by this form of experiment falls outside the range of the present investigation.

In about one-half of the recent investigations recorded in the literature, the influence of supplementary food is either ignored or is expressly included. This raises at least three points of question—the influence of (a) impurities, (b) food as such, and (c) supplementary carbohydrates. Further, in like proportion, urine findings are omitted, and the investigations deal solely with the indications of blood sugar levels. Each of these several points may be briefly discussed.

In regard to the first, Kraus and Ludwig (19) report experiments in which 100 grams of commercial glucose produced melituria, while double the amount of pure material gave negative results. Recently Folin and Berglund (11b) have emphasized this point. While in practically all of the recent studies, great care was exercised to use only sugars of a demonstrable purity, the use of fruit juices as adjuvants must be regarded as introducing elements of uncertainty, both as regards purity of the resulting mixture and also of the absolute sugar dosage. In this connection, the authors secured a most interesting piece of information in a fortuitous manner. A subject under investigation gave a melituria with 10 grams of galactose dissolved in milk but not in water. The observation is suggestive.

The influence of food upon carbohydrate assimilation has been frequently observed, although the several findings are not uniformly consistent with each other. Jacobsen (17), and Labbe and Theodoresco (20) have reported observations; Folin and Berglund (l. c.) feel that a non-carbohydrate meal is without influence on glycuressis, while Benedict and Osterberg (6d), citing their earlier work with Neuwirth (6c), and analyzing the Folin-Berglund data, reach an exactly opposite conclusion. Without further citation, it may be said that in the light of these conflicting opinions, an element of grave uncertainty can be eliminated by the rigorous exclusion of other food from the test meal. The direct influence of other carbohydrates will be discussed later.

In regard to simultaneous observation of blood and urine findings, in the opinion of the present authors, both may be observed with profit, but of the two, the urine sugar is far more significant. This statement is made with just recognition of its debatable character. In other words, the ultimate criterion becomes the sensitivity of a qualitative chemical reagent. But with a reagent of such proven dependability as that selected, it is felt that by its use a line of demarcation may be established between the amounts of reducing bodies present in every so-called normal urine and those quantities which represent an elimination under a special exciting stimulus. Blood sugar and urine elimination curves lack a common basis for comparison. In the first, a concentration is measured which is a variable, the absolute value changing from moment to moment as the various factors influencing it are more or less actively operative. A static condition may not be attained, certainly not during a period when absorption from the intestine is in process. On the other hand, conditions in the urine are essentially different. Here, through physical limitations, collections can be made only at appreciable intervals. It is to be noted incidentally, that even protracted use of a catheter with continuous flow does not insure the removal of all excreted urine. Only simultaneous bilateral ureteral catheterization could accomplish this result, a condition practically precluded with human subjects.

The material obtained at intervals represents the summation of a large number of widely divergent eliminations. Further, blood is an essential integral part of the functioning body, in contact with active cellular material, itself the medium in which a wide diversity of chemical and physical changes are constantly taking place. On the other hand, the urine as collected from the bladder is an end product, outside of the essential organism and except for possible slow reabsorption with its composition uninfluenced by any other agency than that causing its gradual accumulation. The work of Taylor and Hulton (31) with a twenty-four hour collection of the urine illustrates this sharply, while a more recent paper by Bailey (2) gives additional information.

To conclude, the authors feel that, supplemented by the experience of many others, their own observations show that melituria and hyperglycemia are, in large measure, mutually independent, unrelated phenomena having a point of contact only in a possibly common origin.

The relative merits of the uniform test meal and that proportioned to body weight require passing comment. Body weight is again a summation of varying amounts of widely divergent materials. Certain portions of the human body are directly concerned with the immediate carbohydrate metabolism, others only remotely, if at all. Selecting a few cases from similar etiological groups, one finds that among the G group, B-9, weighing 80.8 kilos, eliminated 1.24 grams of reducing sugar with an exciting dose of 30 grams, while B-40, weighing 44.9 kilos, eliminated 0.70 grams on the same dose. Likewise, B-10 and B-50, weighing, respectively, 46.8 and 110.0 kilos.

show with the first less than 0.20 grams and with the second 0.05 grams on ingesting a test meal of 20 grams. Other cases might be cited. Only two values for the basal metabolism are available—B-40, with minus 15 per cent, and B-50 with minus 17 per cent. With young children Greenfield (15), using levulose dissolved in milk (!), found a complete independence of assimilation limit on body weight. It is highly important that the subject shall be maintained in a resting state during the test. The increased utilization under the influence of muscular work has been observed by several investigators, of whom Graham (14), and Grafe and Solomon (13) may be named among the more recent. Similarly, extremes of heat and cold are to be avoided.

Passing reference has been made to an exhaustive study published by Folin and Berglund (11b) on certain phases of carbohydrate metabolism. In an investigation of such scope, and one in which the experimental findings are of such proven accuracy, the conclusions from so authoritative a source require careful consideration.

The authors have observed blood and urine changes under the stimulus, in the majority of cases, of large doses of a number of carbohydrates of known degrees of purity.

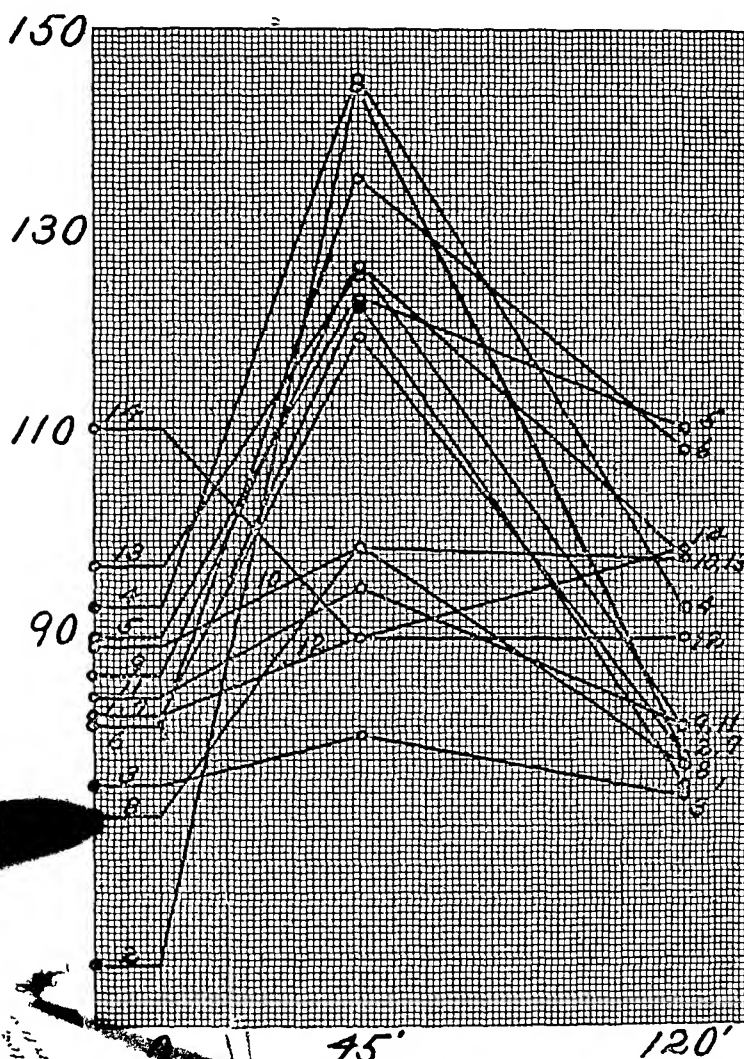
Selecting those conclusions which are germane to the present text, they may be summarized as follows:

Galactose is much less effective than glucose in raising the level of blood sugar. Absorption of sugars by tissues rather than glycogen formation is believed to be the significant factor regulating blood sugar levels. There is no renal threshold for galactose. The retention and utilization of galactose depends upon the amount of available glucose. Hypoglycemia is probably an index of decreased need of sugar transportation. Glycuresis is obtained after every ordinary carbohydrate meal, but not from the ingestion of certain pure carbohydrates, is independent of blood sugar level, and represents the excretion of foreign carbohydrates from various sources.

Since the publication of this paper, three reports have appeared in the literature, all challenging one or more of the conclusions contained therein. The first, by Foster (12a, b), comprises studies on the levels of sugar in finger and vein blood

under the influence of orally administered doses of glucose and of galactose, and an interpretation of the observed phenomena.

Tables and curves are given, recording results with 100 and 200 grams of glucose, 100 grams fructose, 80, 90 and 100 grams galactose, 70 and 100 grams starch, and 10 grams of agar. It is interesting that the experiments with 200 grams of glucose show a peak



Curves of Group T1, super-tolerance dose.

similar results, while with the smaller dose the observed peak was at thirty minutes, with the exception (Expt. 49) thirty minutes after the dose. This apparent anomaly harmonizes with the results of the present writers already discussed. With 80, 90 and 100 grams of galactose, the peak was at one hundred and forty minutes, and with 100 grams at one hundred and fifty minutes—B-10 and B-5 of the maxima in each instance showing a rough

proportionality to that of the exciting dose. As has already been pointed out, the shape of blood sugar curves is potentially misleading. Actual graphic delineation of changing level could be obtained only by the examination of an impossibly large number of samples taken at impossibly short intervals. This is far more true with glucose, with its apparent dynamic action, than with the seemingly less active galactose. As the author gives no results of urine analysis, it is impossible to say how far a melituria assisted in the

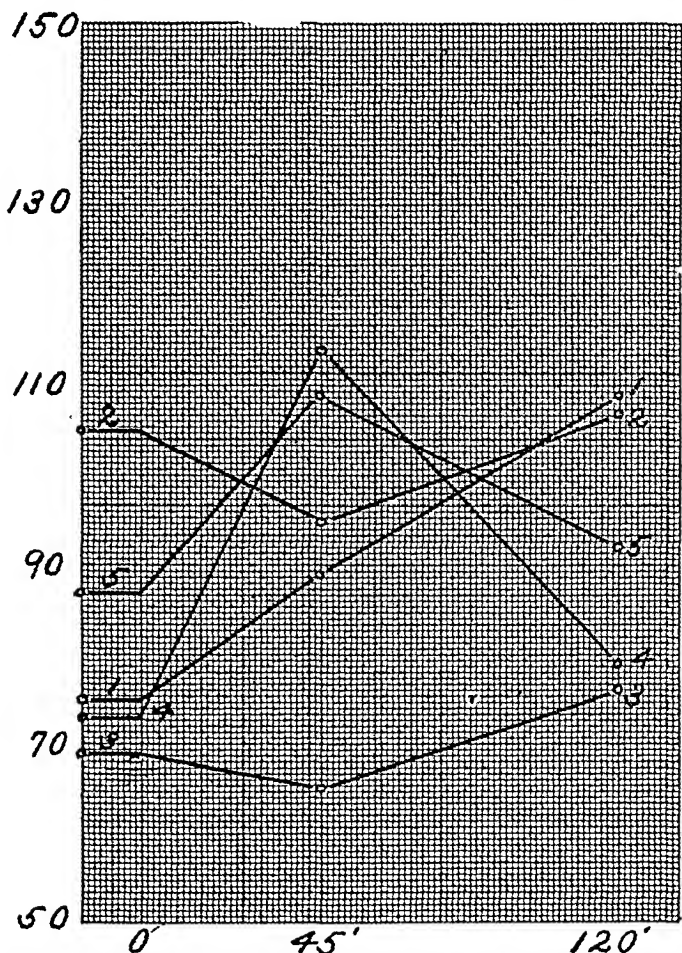


Fig. 2. Blood Sugar Curves of Group T1, sub-tolerance dose.

restoration of the original blood sugar level. The present authors' experience shows that with the galactose at least an active melituria must have existed in these experiments.

The point to be emphasized in regard to these experiments is that with 100 grams of glucose certainly, the test meal was

well below the so-called tolerance threshold, while with normal persons even 80 grams of galactose is far above the assimilation limit. Comparison between the two series of experiments fails of parity of conditions.

One other point of interest presents itself. In all three of Foster's galactose curves, the maximum presents itself at one hundred forty or more minutes after the ingestion of the test meal. In the present authors' series of fifty-six completed curves with super-tolerance dosage, only two have failed to reach a maximum at the end of forty-five minutes. Of the two exceptions, one case, B-57, a pluriglandular involvement, with an exciting dose of 50 grams and an elimination of 0.41, showed progressively 100, 105, and 107 milligrams of sugar. With a sub-tolerance dose of 40 grams, the values with this patient were severally 100, 96, and 89 milligrams. The thought naturally occurs that a maximum was reached in both cases earlier than forty-five minutes. The other patient, Case B-12, having status lymphaticus, showed an almost parallel relationship of 100, 107, and 110. With 20 grams and no glycosuria the curve was normal. Of the twenty-eight complete curves with sub-tolerance dosage, but one failed to reach a maximum in forty-five minutes or less. This case, B-13, was of myxedema of long standing, with a basal metabolic rate of minus 41 per cent. The shape and slope of the observed curve testifies in this single instance to the dominance of the absorption factor. While it is true that the authors' dosages—up to 60 grams—fall short of those administered by Foster, the discrepancy between forty-five and one hundred forty minutes is greater than that between the size of the respective test meals. There is evidently some other factor, as yet undetermined, in the metabolism of galactose, which must be invoked to explain such widely discrepant results.

The second paper, by Benedict and Osterberg (6d), is a direct reply to the Folin-Berglund article. The apparently slight effect of the large test meals of the several sugars is commented on and the well-known anti-diuretic action of large dosage offered as a partial explanation. Further analysis of the data leads them to the conclusion that the principal subject, H. B-d, does not possess a normal metabolic relationship for carbohydrates. This conclusion was reached by the present

writers at the time of appearance of the Folin-Berglund paper, and has received repeated confirmation in the data presented in this paper. A total elimination of approximately 5 grams of reducing substance, even making due allowance for the carbohydrate paradox, would place the assimilation limit for galactose with H. B-d in the neighborhood of 60-70 grams—in short, a greatly increased tolerance. This unusual carbohydrate metabolism must exercise some influence in all of the experiments in which he was the subject, and would seem to affect conclusions made on the assumption of his normality. The work of the present authors is patently open to the same objection, as but few of their experimental subjects were normal in regard to their carbohydrate metabolism. From the comparison, however, of the normals included in the present study with the groups of cases investigated, the authors feel that too much emphasis could readily be given to this factor.

Benedict and Osterberg comment on the evident fact that hyperglycemia is not necessary to produce a glycosuria, and that the observed level of the blood sugar is no criterion for the extent of the glycosuria. The present studies would seem to indicate that a glycosuria once established persists even when the blood sugar has fallen to a relatively low level, a fact that has frequently been observed and recorded by others in a most conclusive manner. In the present case, however, the interval of forty-five minutes between the ingestion of the test meal and the drawing of blood is ample to allow for the rapid establishment of a transitory higher level and the compensatory subsequent fall which could bring the blood sugar to its original level or even below at the time of observation. These points have already received comment in an earlier part of the present paper. Comment may be made upon the apparently anomalous results obtained where the effect of 100 grams of galactose is compared with that of 100 grams each of galactose and glucose. A more rapid absorption of the glucose fraction is postulated as the explanation. This point will be discussed in connection with the third paper, which contains data most pertinent to the question.

While this article was in process of revision, a series of observations has appeared [Bodansky (8)] which bear directly upon questions raised in the two foregoing papers. The writer



has reinvestigated certain of these questions, using dogs as his subjects, and as his method the oral administration of doses of 3 grams per kilo, respectively, of dextrose, levulose and galactose. He finds, under these conditions, the same delayed maximum in the blood sugar curve with galactose which was ob-

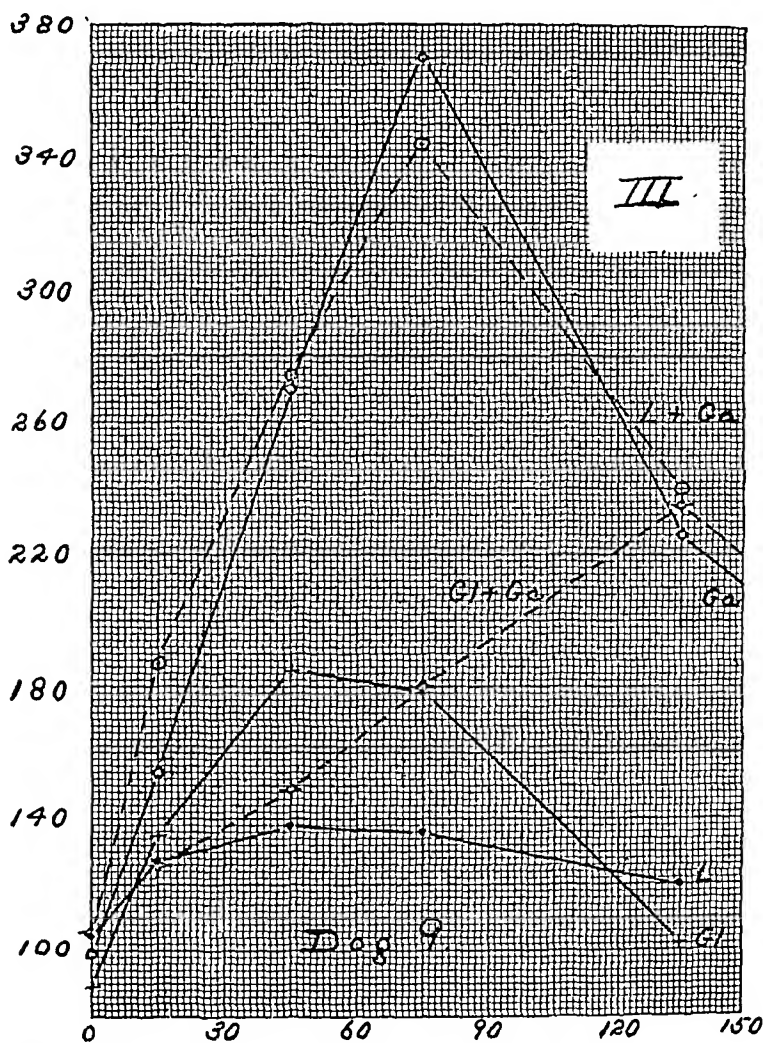


Fig. 3. Effect of Mixed Carbohydrate Feeding (Bodansky).

served by Foster, although the mean of 20 series of observations shows the peak at seventy-five minutes and an incipient fall at one hundred thirty-five minutes.

There exists a fairly extensive literature on the assimilation limit of various animals for the several carbohydrates, the results of which, in the main, show a sufficient measure of concordance to

render a detailed analysis unnecessary. Selecting Allen's observations as comparable, it is stated by that author that while the subcutaneous tolerance in dogs is of the order of 7.9 grams per kilo for glucose, the galactose tolerance is less than 1 gram per kilo. This ratio is substantiated by numerous other observers. On this basis, and with recognition of the influence of the magnitude of the exciting dose on the blood sugar curve, the writer should have given from 20 to 30 grams per kilo of glucose to duplicate the massive super-tolerance dose of galactose used. Even assuming Benedict's

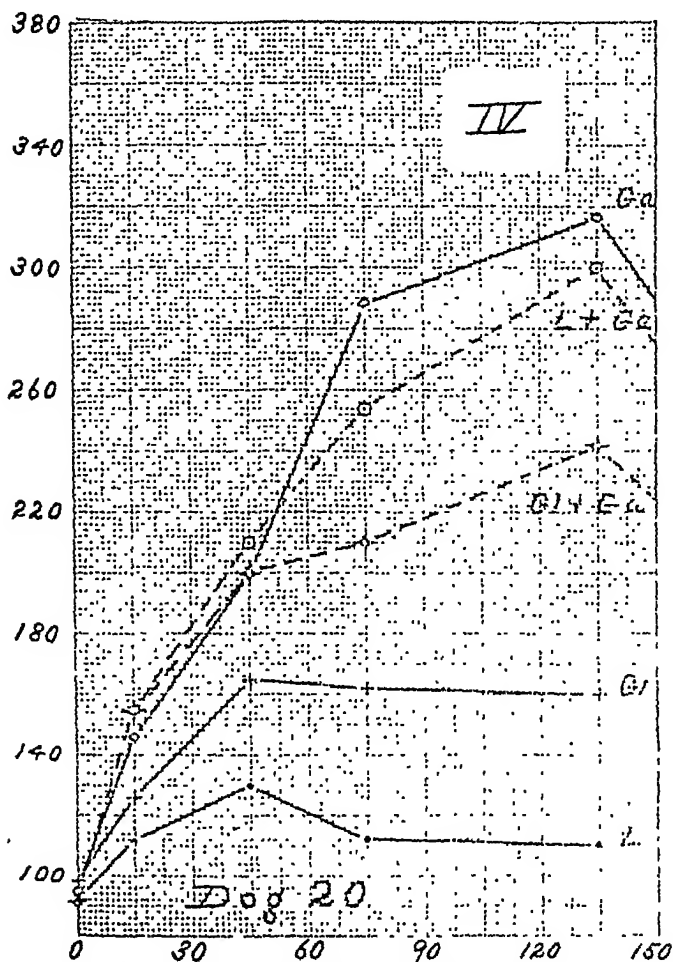


Fig. 4. Effect of Mixed Carbohydrate Feeding (Bodansky)

figure—5 grams per kilo—for glucose subcutaneously as more nearly correct the minimum dosage would have been not less than 15 grams per kilo. The impracticability of this procedure is obvious. While oral tolerance is somewhat greater than subcutaneous, Benedict's dog, with 17 grams per kilo by the latter route, died in seventeen

hours. While no parity can be established, the fact is suggestive of potential disturbance to the organism should such massive doses be retained.

A second point on which the author's data bears most illuminatingly is that touched upon in the preceding discussion—namely, the influence of ingested glucose (and fructose) upon the absorption of galactose. Bodansky gives two tables (III and IV) in which these influences are studied. Reduced to graphic form the relationships are very apparent (Curves III and IV).

It is to be assumed that these protocols are representative and that they picture the general mechanism. In both instances, levulose produces a slight, glucose a more marked, increase in blood sugar with the point of inversion of all curves at forty-five minutes. Galactose, on the other hand, shows a far greater increase, with the maximum in one case at seventy-five, in the other at one hundred thirty-five minutes. With the combined test meals, however, the maximum in three instances is at one hundred thirty-five minutes and in the fourth at seventy-five. Even closer analysis is profitable. With dog No. 9 (Table 3) levulose gives a flat curve, glucose a definitely more acute rise and fall. The combined levulose-galactose curve approximates that for pure galactose, while the glucose-galactose shows an essentially less marked change—and with a maximum appearing at one hundred thirty-five minutes. With dog 20, the results are even more striking. Again the levulose-galactose curve approximates pure galactose, while the glucose influence again produces a curve in intermediate position.

In the light of these curves, Bodansky's statement that with dextrose and galactose together (with Dog 9) "the hyperglycemia produced is not much more marked than that following the ingestion of glucose alone," does not seem warranted.

Further, until more light is shed upon the mutual influences of sugars fed together, the present authors take exception to Bodansky's statement that "levulose . . . should exert an even greater effect (than glucose) in depressing galactose hyperglycaemia." From the curve it is evident that the sugar which intrinsically exercises (for whatever reason) the least influence on the blood sugar level, exercises the less disturbing effect on the behavior of the galactose. With the glucose, on the other hand, the resulting curve is patently influenced by the mutual action of each sugar upon the other. Further support of this interpretation is found in Table 5, where results are given of the amounts of sugar excreted under the several conditions. The Folin-Berglund experiment given in their Table XVI would seem to lend support to this general idea if blood levels and rate of sugar excretion be plotted simultaneously. As the glucose influence begins to disappear, that of the galactose manifests itself.

In all these cases the melituria excited by the addition of fructose exceeds that produced by the glucose addition. Further, the amount excreted in two cases approaches that eliminated under the influence of galactose alone, and in the third—with a smaller dog—even exceeds it.

As the author points out, lower blood sugar level could be invoked to explain these observations, but the present authors

feel that the results of their experimental work show that, as has already been stated, while melituria and hyperglycemia may have the same initial exciting cause, they are relatively separate phenomena and are not necessarily mutually interdependent. Another element which adds to the obscurity of the problem lies in the different oxidation velocities of the several sugars. Galactose has been shown to give results less than the truth in comparison with a glucose standard. What the algebraic sum would be when to normal blood dextrose is added both galactose and levulose, may well give rise to pleasing speculation.

To revert briefly to the Folin-Berglund paper: the conclusion in regard to the influence of galactose on blood sugar levels has been shown to be apparently true only in a certain number of cases, and in these a failure to observe the maximum seems to be the probable cause.

To the conclusion that there is no renal threshold, the authors can subscribe only in part. The bulk of the evidence, it is true, would seem to indicate that there is some leakage of a reducing substance through the kidneys under the stimulation of even small doses of the sugar. But it remains to be shown that this "glycuresis," or better, "melituresis," is due to galactose. The influence of impurities observed by Kraus and Ludwig and others, and demonstrated so conclusively in the Folin-Berglund studies, might again be invoked. Further, the evidence from all sources would seem to point most conclusively to the presence of other reducing bodies, and if these are increased by sub- and super-tolerance doses of glucose, why should not galactose exercise a similar action? The authors feel that in all previous studies of the comparative effects of several carbohydrates, the lack of emphasis on the relation of the selected dosages to those which will produce demonstrable meliturias, has eliminated an absolute basis of parity in the observations. Also, the intervals between blood samples makes the apparent absence of a hyperglycemia in certain cases a matter rather of uncertain inference than of observation. The more rapid fall observed with the larger of two doses of glucose might well have a bearing in galactose experiments where massive super-tolerance meals are given. Finally, the fact remains that with groups of so-called normal persons there

exists an approximately constant dose of galactose which excites a demonstrable melituria; that in certain pathological states in which the so-called threshold has been found to deviate from the accepted normal when tested with dextrose or fructose, like deviations are observed when galactose is substituted.

#### 8. TISSUE ABSORPTION AND MAMMARY INFLUENCE

The point in the Folin-Berglund paper which stands out most saliently from the writers' point of view, and in which is to be found the most stimulating and suggestive concept, is that which deals with tissue absorption as the main and glycogen formation the secondary, and in measure sequential, regulator of blood sugar levels. With this is clearly associated the apparent influence of a second carbohydrate on the behavior of the first. That glucose definitely does influence the utilization of galactose has been observed by several earlier writers, and is certainly implicit in the disproportion of the so-called thresholds for galactose and lactose. Bodansky's work throws added light in that it confirms the glucose influence and demonstrates that levulose, with an apparently different relation to the organism, exercises a divergent and notably smaller effect upon the galactose utilization. Space does not permit an elaboration on this topic at the present time. Investigations are under way from which it is hoped some pertinent information may be drawn. To return briefly to the main thesis—namely, tissue absorption: The present authors, in the course of their investigations, have elicited certain facts which they feel are of definite bearing on this question. The investigation is still in progress and report at this time must be preliminary, with all conclusions highly tentative. With this statement the facts in question may be presented briefly.

1. The so-called threshold of tolerance for galactose is higher for women than for men, the average values being about 40 grams for the former and 30 grams for the latter. The only parallel observation is in a table from Quarta, cited by DeFilippi (9), giving results with dogs. The validity of these findings is denied by Allen (1).

2. In the mammary gland, the female has a special mechanism for the synthesis storage and utilization of galactose of which the male is devoid.

3. In these cases where there is a primary failure of the gonads, whether as the result of functional disturbance, of physiological change or of surgical ablation, there is a lowering in the so-called tolerance threshold of the female which finds no counterpart in the male.

4. The well-known lowering of the tolerance threshold during pregnancy might be due either to a suspension of gonad function or equally, if not more probably, to a saturation of the tissues in question.

5. Data are lacking on young children in the prepubertal period before the development of the secondary sex characteristics. In the excellent article by Meyer and Stern (25), a number of data are given, but they are too few to warrant any conclusion. This phase, as well as the influence of pregnancy, are now under investigation.

From the foregoing it seems to be established that the normal adult female has a capacity for utilizing galactose, which, lacking in the male, is intrinsically connected with sex. Further, with a retrogression of the secondary sex characteristics, induced by primary failure, this special power is lost. It is not, therefore, unwarrantable to conclude that the mammary gland may possess direct power of absorption or utilization, and that this fact may suitably be adduced as a support of the Folin-Berglund tissue absorption concept.

## 9. CONCLUSION AND SUMMARY

Before summarizing the results of this experimental study, one point should be emphasized, namely, that the shape assumed by the conventional blood sugar curve is essentially determined by the relationship of the exciting dose to the so-called threshold of tolerance. So-called normal curves are produced by super-tolerance doses of moderate degree. The flat or even inverted curves of hypofunction are the result of sub-tolerance dosage. The characteristic diabetic curve is characteristic solely because the usual exciting dose is far above the conventional threshold of tolerance—in other words, an heroic super-tolerance dose (see Foster's curves), and the debatable intermediate curves that fall between the progressive diabetic rise and the definite sequential downward trend of the normal are only expressions of the relation of the individual dose to

the individual tolerance threshold. In other words, by a suitable selection of dosage, any so-called diagnostic curve may be produced with the so-called normal individual. The significance of the diabetic curve depends not upon its characteristic shape, but upon the fact that 100 gms. of *glucose* represents a massive super-tolerance dose.

The results of this investigation may be briefly summarized as follows:

1. The velocity coefficient of reduction by galactose is appreciably less than that of glucose. Hence all curves based on copper reduction methods and dealing with mixtures of the two give apparent values that are less than the truth.

2. Test meals of urea with observation of blood levels and urine elimination, show that delayed absorption apparently plays little or no part in cases showing increase in the so-called tolerance threshold.

3. Rapidity of elimination of urea is not conditioned solely by blood urea level, and the inference is drawn that determinations of blood and urine urea are measurements of related but not mutually wholly dependent phenomena.

4. No blood sugar curve determined by straight line interpolation between isolated points gives more than a first approximation of the progressive change of blood sugar levels, and in many cases is definitely misleading.

5. The observed degree of hyperglycemia and of melituria show a complete lack of relationship. They are to be regarded as two parallel phenomena having a potentially common origin, but being quantitatively mutually independent.

6. A general relationship between the type of curve and the magnitude of the exciting dose in connection with the so-called tolerance threshold has been observed.

7. The anomaly of an inverse relationship of size of exciting dose to the magnitude of the observed hyperglycemia has also been recorded in certain cases.

8. Certain criteria for the administration of carbohydrate test meals have been defined and emphasis is laid upon the necessity of using equivalent doses when several sugars are to be compared.

10. The tissue absorption concept of Folin and Berglund has been discussed and certain observations on the potential

influence of the mammary gland on carbohydrate utilization, adduced in its support.

In conclusion, the authors take much pleasure in acknowledging their indebtedness to their colleagues, who have referred patients for these studies, and in particular to the subjects themselves for a helpful interest and most gracious spirit of co-operation.

Especial thanks are gladly rendered to Miss Bertha S. Wiener, to whose competent hands have been intrusted many of the measurements here recorded.

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# IS THE TADPOLE TEST FOR THYROID VALID?

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It is a matter of common observation to clinicians and experimentalists that various samples of commercial thyroid preparations may differ considerably with regard to their physiological activity. The value of this gland as a therapeutic agent in the treatment of hypothyroid cases, has of late years been considerably increased by the adoption of a method of standardizing different preparations on the basis of their iodine content.

However, it requires but little reflection to see that such a chemical method is not entirely satisfactory for determining the physiological effectiveness of thyroid preparations. Only a certain special kind of iodine complex is active, and to date no other type of iodine compound, inorganic or organic, is known that is capable of simulating in a qualitative or quantitative manner the effects produced upon mammalian metabolism, and on myxedema and cretinism, by the idoine complex peculiar to the thyroid gland, i. e., thyroid iodine. Consequently, the iodine content of thyroid preparations should refer only to thyroid iodine, but unfortunately such is not the case. A large part of the iodine contained in the thyroid is said to exist in inactive form and is apparently united with amino acid complexes, possibly representing intermediate steps in the synthesis of the active hormone.

It has been shown (1) that hyperplastic thyroids extremely low in iodine content are capable of absorbing large amounts of iodine both *in vivo* and *in vitro*, and when potassium iodide is injected into the circulation of an animal with goitrous or hyperplastic glands the iodine is absorbed by the thyroid practically as soon as it reaches the gland. Such thyroids when assayed can be made to show any per cent of iodine. But despite the high iodine content such glandular tissue has little thera-

peutic value, because the iodine present is not thyroid iodine, i. e., in thyroxin form. A certain time is required for the thyroid to convert the iodine it receives into the combination peculiar to its hormone.

Since Gudernatsch's discovery of the remarkable effect of thyroid upon amphibian metamorphosis, several investigators have suggested that this reaction be employed as a method of physiological assay for testing the activity of thyroid preparations, as a supplement or even substitute for the present method of standardization by means of the iodine content.

Romeis (2) was the first to propose the use of the tadpole test as a means for standardizing commercial thyroid and iodothyrene preparations. He observed great variations in the activity of the preparations tested, as manifested by the rapidity with which the material induced metamorphic change in frog larvae when fed, and stated that his results with amphibian larvae agreed with similar experiments on dogs, and with clinical observations. He did not compare the activity of the different preparations with their iodine content. Lenhart (3) showed that desiccated thyroid when fed to tadpoles induces effects on their growth and differentiation in proportion to the quantity administered and the amount of iodine present. He suggested that the tadpole reaction to thyroid might serve as a biological test for the activity of thyroid preparations, superior even to chemical methods.

Rogoff (4) made use of the action of thyroid upon amphibian metamorphosis to assay the physiological value of various commercial thyroid preparations. In his paper he advances cogent reasons why the present method of standardization of thyroid by determination of its iodine content is not an entirely reliable indication of its therapeutic value, and suggested the tadpole test as a method of physiological assay.

Jensen (5) proposed the use of the axolotl for the standardization of thyroid preparations. As is well known, this animal is the paedogenetic larvae of *Amblystoma tigrinum*, and readily responds to thyroid administration by metamorphosis. Various commercial extracts of thyroid and iodothyrene were tested on

axolotls and it was found that the efficiency of the preparations used was not directly proportioned to their iodine content.

Hogben and Crew (6) employed the axolotl as a means of determining the degree of physiological activity of fetal and embryonic ox and sheep thyroids. A single meal of fetal thyroid was fed to axolotls, and if metamorphic changes were initiated it was regarded as demonstrating the fact that such glands were actually building up their active products.

It is quite evident that the first four authors mentioned regard the present method of standardizing thyroid preparations by their iodine content as unsatisfactory, but it is questionable whether the suggested utilization of the metamorphic changes of amphibian larvae as a method of physiological assay of thyroid activity is likely to prove any more satisfactory. In fact the writer is inclined to doubt if the tadpole test is really valid, and believes that it is really a test for a peculiar type of organic iodine, and not specific for thyroid iodine. The following experiments invalidate the tadpole test for thyroid activity and preclude the employment of these animals for physiological assays of thyroid products (7).

The three blood proteins, serumalbumin, serumglobulin and fibrin, have little if any effect upon the differentiation of thyroidectomized and hypophysectomized frog tadpoles. However, if these substances are iodized properly they become highly active metamorphosis-inducing agents when fed or injected. The addition of the iodine to the molecule of these proteins transforms an inactive substance, insofar as frog metamorphosis is concerned, into an agent which simulates the thyroid hormone (although the acceleration of metamorphosis is not so rapid) in the effect produced upon anuran differentiation. Iodized casein behaves in a similar fashion, although this protein does not appear to be quite so active as the others mentioned. Iodogliadin if fed in large quantities for two months or more will metamorphose hypophysectomized tadpoles. The metamorphosis-inducing activity of this vegetable protein is distinctly less than the other iodized proteins tested. However, the activity of any one of these proteins depends upon the method of iodization. The looser the combination effected between the iodine and the protein, the less the activity upon differentiation. In

contrast to iodogliadin, the vegetable protein edestin is an active metamorphosis inducing agent when properly iodized, although apparently not so active as the blood proteins mentioned. Rogoff (8) states that iodized egg albumin (fresh egg white) shows some activity when fed to normal tadpoles, but that the activity is not very great.

The writer has not found iodalbumin (Parke, Davis & Co.) nor iodocasein (Mulford & Co.) very active in inducing metamorphic change. In both of these commercial preparations of iodized protein the iodine is in loose combination and is very easily split off the protein molecule; some specimens seem to be more active than others.

The structure of the protein molecule is as yet unknown; consequently the nature of the iodine linkage is undetermined. However, one of the amino acids, tyrosine, has been successfully iodized and is known to be an effective agent in inducing the metamorphosis of both thyroidless and hypophysectomized tadpoles. Tyrosine is inactive, dibromotyrosine is inert, but diiodotyrosine is very effective in accelerating transformation. It is clear from the experiments upon iodotyrosine that the effective agent in amphibian transformation is the iodine in the molecule, bromine cannot be substituted for it and the tyrosine remain active. Moreover, the nature of the iodine linkage in diiodotyrosine is known and this amino acid is not chemically related to thyroxine, the active principal of the thyroid. Perhaps even more interesting in this connection is the fact that tyramine, the decarboxylated product of tyrosine, when iodized, is an active agent in producing metamorphosis (9). The iodine linkage in tyramine is the same as in tyrosine, i. e., to the 3rd and 5th carbon atoms of the benzene ring.

Investigators who have worked upon this phase of the problem agree that iodized proteins such as iodoserumglobulin, albumin and casein show little if any thyroid-like effects upon mammalian metabolism, nor does the administration of such substances alleviate the symptoms of myxedema or cretinism.

Oswald (10) studied the physiological properties of several iodized proteins and compared them with thyroid. He found that iodocasein, iodoserumalbumin and diiodotyrosin do not exert thyroid-like effects when administered to mammals.

Hellin (11) reported that iodoalbumin and nucleo-albumin prepared from the spleen are inactive when given to mammals, and Blum (12) states that iodoalbumin has practically no effect upon metabolism.

Strouse and Voegtlin (13) did not observe any thyroid-like effects upon the nitrogen metabolism or on the blood pressure of normal dogs, nor was there any favorable effect on the condition of myxedematous and cretinous mammals following administration of diiodotyrosin.

It is evident that the substances which accelerate metamorphic change in amphibians, thus simulating the activity of the thyroid hormone in this vertebrate group, do not exert thyroid-like effects when administered to mammals, at any rate insofar as metabolism is concerned. Perhaps the most convincing evidence that the effect of thyroid upon amphibian metamorphosis and upon mammalian metabolism is due to different chemical groupings in the thyroid hormone is that adduced by Kendall (14) and the writer (15) on the acetyl derivative of thyroxin. The following experiment was recently performed by the writer. Two normal, healthy adults took 10 milligrams of crystalline thyroxin intravenously; a profound physiologic response, comparable in every way to that evoked by excessive thyroid feeding, was evoked, the effect lasting about six days. Several weeks later the same two subjects received an intravenous injection of 10 mg. of thyroxin in which the hydrogen of the imino group had been replaced by acetyl. The injection produced no response whatever. Kendall earlier had noted that acetyl thyroxin when injected into dogs produced no physiologic response, whereas an equal amount of thyroxin did produce a profound response lasting some time. The fact that when the hydrogen of the imino group in thyroxin is replaced by acetyl the substance loses its physiologic activity and there follows no demonstrable effect upon mammals emphasizes the importance of the imino group and minimizes the importance of iodine in the molecule insofar as the physiologic effect upon mammals is concerned. However, both thyroxin and the acetyl derivative are highly active agents in inducing metamorphosis of thyroidless and hypophysectomized amphibians. The con-

clusion seems justified that the physiologic effect of thyroxin and thyroid in mammals is due to the CONH group within the molecule, because when the hydrogen of this group is replaced by acetyl the thyroxin becomes inert, yet the iodine complex remains unchanged. On the other hand, it is the iodine complex in the molecule which is effective in accelerating amphibian metamorphosis. The reasons for this conclusion are obvious: (1) the acetyl derivative of thyroxin is highly effective despite the change in the CONH group which is rendered inactive; (2) iodotyrosin is highly effective in inducing amphibian metamorphosis and there is no CONH group in this substance; (3) certain iodized proteins which are inactive when administered to mammals are highly active in metamorphosing amphibians.

Now what is the bearing of this evidence upon the validity of the tadpole test for thyroid? Simply this, that the tadpole test is a reaction to a certain type of organic iodine complex found in the thyroid and gives no clue to the activity of or even presence of other chemical groupings within the molecule, for instance the CONH group, which alone (though probably in conjunction with iodine) has an effect upon mammalian metabolism and upon myxedema and cretinism. Acetyl thyroxin gives a positive tadpole reaction, but this substance has no effect upon myxedema or cretinism.

It is evident that the use of tadpoles for testing the physiological activity of thyroid preparations is unsatisfactory. Thyroid samples, giving a very positive test when fed to thyroidectomized tadpoles, might be totally inert when fed to mammals insofar as the metabolic rate and the alleviation of myxedema and cretinism are concerned.

It is unjustifiable to assume that the iodine containing complex responsible for amphibian transformation is identical with that which has to do with mammalian metabolism. Iodine seems essential to both chemical groups, i. e., the one responsible for mammalian metabolism and the group responsible for amphibian metamorphosis, but in mammals other constituents of the molecule such as the CONH complex are of equal or even greater importance.

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# Editorial

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## THE ROLE OF IODIN IN THE TREATMENT OF GOITER

When competent observers appear to obtain conflicting results from the administration of a drug, it is wise to reserve judgment. Future work sometimes explains the discrepancy. Iodin has been employed in the treatment of goiter for many centuries. Roger, of the University of Salerno, about 1170 recommended the use of ashes of sponge and seaweed, and Coindet in 1820 pointed out that the active substance in such concoctions was iodine. In the latter part of the nineteenth century its use in the treatment of thyroid disease became quite widespread. Especial benefit was noted in the treatment of endemic goiter and particularly in its prevention, and this aspect of its usefulness was finally conclusively demonstrated on a large scale by Marine and Kimball in their studies of school children in Akron, Ohio. Its indiscriminate use in goiter generally became discredited, however, and the great Kocher warned the medical profession of its positive harmfulness at times in converting a non-toxic into a toxic goiter ("Jod-Basedow"). His influence on medical practice was so powerful that its use to any appreciable extent outside of "simple endemic goiter" was practically abandoned. Any evidence of hyperthyroidism was considered a contraindication to the administration of iodine. Despite this injunction, some clinicians could not be dissuaded from treating hyperthyroid patients with some form of iodine and reported, ever now and again, decided improvement. It was difficult to reconcile such statements with repeated evidence of its danger.

Meanwhile, amidst this confusion, Plummer made his masterly contribution, differentiating between two thyrotoxic syndromes—adenomatous goiter with hyperthyroidism, and exophthalmic goiter (Graves' disease). He was able to prove beyond question that although these two syndromes had several symptoms and signs in common (such as tachycardia, tremor and increased basal metabolism, that they were pathologically distinct,



THE INTERNAL SECRETIONS. Arthur Weil, translated by Jacob Gutman. N. Y., 1924. Macmillan Co., 3 ed., pp. 287. Illus.

Weil, a physiologist, has approached the presentation of endocrinology from a somewhat different angle than the majority of text books on the subject. Instead of considering the various ductless glands separately, describing their functions and the clinical syndromes that are the result of abnormal function, the author has attempted an aeroplane view over the field in an effort to correlate the various glands in a unified manner with reference to particular body functions. Some of the chapter headings will illustrate his conception: "The Circulation of the Blood," "Respiration and Voice Production," "Metabolism," "Growth and Bodily Form," "Reproduction," "The Sexual Impulse," "The Mind and the Internal Secretions," "The Chemistry of the Secretions," etc.

The first edition was published toward the close of 1920. That a third edition appears so soon is obvious evidence of popularity, which is further attested by translations into Spanish, Russian, Japanese, and now into English. The translator deserves credit. He has avoided a literal clumsy rendition from German to English, and has produced a version gracefully phrased and pleasant to read.

No bibliography is included, which is a wise decision—it would either suffer from incompleteness or else tremendously enlarge the book and merely duplicate what has already been done exhaustively in the works of Biedl and Barker, one of which has 500 pages and the other 700 pages of reference.

The third German edition (of which this is a translation) appeared in January, 1923. Consequently very important researches, such as insulin, Evans and Smith's work on the hormone of the anterior lobe of the hypophysis, and Allen and Doisy's work on the ovarian hormone are not included.

This book can be genuinely commended for perusal by medical students and practitioners, especially if it be understood that it is not a short cut to diagnosis and treatment. It is a welcome exception to some of the fantastic endocrine twaddle that has appeared in recent years.—II. L.

THE BIOLOGY OF THE INTERNAL SECRETIONS. Francis X. Dercum, M.D., Ph.D. W. B. Saunders Co., Phila. & Lond., 1924. pp. 241.

This is an interesting essay on the internal secretions treated from a biological and philosophical viewpoint. There is no attempt made to touch the clinical side.

The author makes much of the vagotonic and sympathicotonic systems and elaborates upon several theories based upon these viewpoints. According to him, thymic asthma and thymic death are toxic conditions due to the action of a toxic agent secreted by the epithelial tissue of the thymus, this action being vagotonic.

As an example of the philosophical explanation of the parts played by the glands of internal secretion, Dercum states that the failure of sex development probably occurs when the organism as a whole (rather than one or more special glands) fails to reach the normal level, when the intensiveness of the chemical and physical processes inherent in the germ plasma has not been sufficient to lead to the development of a complete and normal organism.

He asks, can it be that after all the cause of malignancy is biological and that the mystery lies in the internal secretions? and then answers his own question by stating that the cause is not to be sought in some dietary or other fault but in a general reduction in the biological level, this reduction ensuing as a result of the unprecedented strains of modern civilization. If the organism is inadequate to meet them, glandular failure, glandular exhaustion and glandular imbalance result. The breakdown may occur primarily in the parasympathetic or sympathetic groups, but in women it appears to occur with especial frequency in the reproductive group. Mental derangements and deterioration are also due to involvement of either or both of these two groups.

All in all, the book is a very interesting philosophical discussion of the subject for the student of endocrinology. It is apparently not written for the general practitioner.

—M. B. G.

**BASAL METABOLISM. DETERMINATION OF THE METABOLIC RATE IN THE PRACTICE OF MEDICINE.** John T. King, Jr., M.D. Williams & Wilkins Company, Balt., 1924, pp. 118.

In this book Dr. King has briefly summarized the present knowledge of basal metabolism, particularly in its application to clinical medicine. After a very brief treatment of the history of metabolism, he discusses the physiology of the subject. Under this heading the effect of the various endocrine glands upon the metabolic rate is discussed, the various methods for determining the basal metabolic rate are enumerated, and the advantages and disadvantages of each method briefly discussed. Dr. King favors the use of the carbon dioxide method in clinical work, although he points out that this method is inaccurate, and consequently should not be used in cases where the respira-

tory quotient is apt to be abnormal. Since the book is not a laboratory manual, all details in regard to apparatus and methods are omitted.

Other subjects treated are the pharmacology and chemistry of heat production, the anatomy of the thyroid gland, and metabolism in hyperthyroidism and hypothyroidism and under other pathological conditions.

In spite of its brevity (exclusive of tables there are only 92 pages), the book contains a large amount of information that should be of great practical importance to practicing physicians. It should serve as an excellent introduction to the subject for any one who is interested in the field of metabolism, and the appended bibliography, in which are listed nearly three hundred different books and articles, suggests ample reading of a more detailed character for those who care to go into the subject more thoroughly.—F. A. HITCHCOCK.

LES CARACTERES SEXUELS ET L'HORMONE SEXUELLE. Chr. Champy, Paris, 1924, G. Doin, pp. 372.

A very sound and personal review of the problem of sex characteristics. Although histological technique has been used widely, the question is studied with a broad physiological mind. The sex hormone is compared to that of the thyroid and proves to act, in warm-blooded animals, according to the "all-or-none" and "minimum of efficacy" laws. Great stress is laid also on the nutritive conditions which control to a great extent, in lower animals, the onset of the secondary sex characteristics. The latter result from a dysharmonic growth of special organs or tissue zones of the body. The growth rate of them is accelerated with electivity and uniformity by the sexual hormone. Consequently, the idea of a specific catalyser is suggested. The book is crowded with facts and documents of interest for those specializing in that kind of research. It forms an important contribution to our knowledge of the incertory function of the sex glands.—N. GOORMAGHTIGH.

# Abstract Department

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Acute adrenal insufficiency from irradiation of a tumor in a case of Addison's disease (*Insuffisance surrénale aiguë par irradiation d'une tumeur chez un Addisonien*). Arrillaga (F. C.) & Izzo (R. A.), *Compt. rend. Soc. de biol. (Par.)*, 1924, **91**, 27.—T. C. B.

Compensatory hypertrophy of the suprarenals. Boycott (A. E.) & Kellaway (C. H.), *J. Path. & Bacteriol. (Edinb.)*, 1924, **27**, 171-180.

Young rabbits of about 1 kilo (about 3 months old) were taken by litters and in about half of each litter the left adrenal was destroyed, in 7 litters (with 14 surviving animals and 9 controls) by excision and in 5 litters (9 experimental and 11 controls) by ligating the blood vessels to the left adrenal. The latter method was tried with the idea that the absorption of the necrosed gland might stimulate the growth of the other. The experimental and control animals were kept together under identical conditions. They all did well and no difference could be observed between them in rate of growth or general health. They were killed when they had reached about full growth, some 7 to 9 months after operation, the others after 12 months. The adrenals were weighed fresh, after drying and after defatting. To estimate the bulk of the medulla, the fixed gland was cut in serial frozen sections about 100 to 120 microns thick, the sections drawn by projection and the drawings measured with a planimeter. As a result of these observations it was concluded that destruction of one adrenal in the rabbit is not followed by hypertrophy of the other gland.—J. P. S.

The role of adrenal secretion in the chemical control of body temperature. Cannon (W. B.) & Querido (A.), *Proc. Nat. Acad. Sc. (Balt.)*, 1924, **10**, 245-246.

The denervated heart was used as an indicator of adrenal secretion, and it was found that cold accelerated the heart beat from 12 to 43 per cent. This acceleration did not occur if the adrenals were rendered inactive.—T. C. B.

Increase of adrenal secretion in fever. Cannon (W. B.) & Pereira (J. R.), *Proc. Nat. Acad. Sc. (Balt.)*, 1924, **10**, 247-248.

Fever was induced in cats by the injection of dead typhoid bacilli and the rate of the denervated heart taken. The rate is much faster in animals with the adrenals intact than in those where the

activity of adrenals is destroyed by removal of one and denervation of the other.—T. C. B.

**A sympathetic and adrenal mechanism for mobilizing sugar in hypoglycemia.** Cannon (W. B.), McIver (M. A.) & Bliss (S. W.), *Am. J. Physiol. (Balt.)*, 1924, **69**, 46-66.

"Hypoglycemia reactions" are evidence of sympathetic activity, and a natural inference is that adrenal secretion might be increased, and mobilization of sugar from the liver would be a natural consequence. This would lead to an automatic recovery from the disturbed equilibrium. Cats with denervated heart were used. As the blood sugar begins to fall after insulin, it reaches a critical point at which the rate of the denervated heart begins to accelerate, and this continues until a maximum is reached. This point lies between 110 and 70 mgm. of glucose per 100 cubic centimeters of blood in animals under chloralose; between 80 and 70 mgm. in unanesthetized animals. If the adrenals are removed there is no acceleration. If not too much insulin has been given the increase of heart rate may be followed by an increase in the percentage of sugar and a fall of heart rate. It is pointed out that the mechanism protecting the body from dangerous hypoglycemia probably operates in two stages—a primary stage with adrenal secretion and a mobilization of sugar from the liver; and, if this proves inadequate, a secondary stage in which these activities are intensified to the point of convulsions.

—T. C. B.

**The reaction to adrenalin in man.** Lyon (D. M.), *Quart. J. Med. (Oxford)*, 1923, **17**, 19-33.

This study is based upon the response to a subcutaneous dose of adrenalin, in 50 observations made on some 35 subjects. Local and general reactions follow such injections. Locally, a small pale area appears just proximal to the needle mark. This patch increases in size for an hour or two, and may still be visible three or four hours later. It has a rough goose-skin surface, is perfectly blanched, and is usually surrounded by a narrow zone of congestion. The general reaction includes palpitation, rise in blood pressure and augmented blood flow, together with increase in pulmonary ventilation, oxygen consumption and carbon dioxide output. These changes progress nearly synchronously. The characters of the reaction differ considerably in different individuals. The response may be slight, moderate or marked in degree, rapid or slow in onset, short-lived or persistent in duration. The type of reaction depends to a great extent upon the rate of absorption of the drug, and also on the "sensitiveness" of the patient. In a great majority of instances a fall in diastolic blood pressure follows the giving of adrenalin. The effect on pulse rate is much less regular in character and is more easily influenced by outside conditions than any of the

other responses. In all of the cases in this series adrenalin caused an increase in pulse pressure. The maximum increase is reached at the same time as the greatest rise in the systolic pressure. The changes in blood sugar were made the subject of separate observations in order to avoid the effect of over-ventilation due to painful venipuncture on the other reactions. In these cases doses of 1.0 cc. of adrenalin were employed in order to secure a considerable rise in blood sugar. Samples of venous blood were taken at 10 minute intervals. The sugar in the blood was found to increase slowly; the maximum occurs when the other reactions have nearly passed off, and the subsequent decline is very gradual. When the patients are examined from the point of view of the disease present, the changes are not found especially characteristic. Untreated hypothyroid subjects show poor reactions, hyperthyroid subjects marked reactions, and in diabetes the character of the response is influenced by the nature of the diet during the preceding days.—J. P. S.

The effect of ingested adrenalin chloride on basal metabolism. Hitchcock (F. A.), *Am. J. Physiol. (Balt.)*, 1924, 69, 271-278.

In 10 out of 11 experiments on men the oral administration of adrenalin was followed by a rise in metabolic rate. The average increase was 6.9%.—T. C. B.

On the relation of the active bodies of the stellate ganglion to adrenalin (*Sur la relation du corps actif des ganglions étoilés avec adrénaline*). Gutowski (B.), *Compt. rend. Soc. de biol. (Par.)*, 1924, 90, 1469-1470.

From experiments with extract of the sympathetic ganglion (Stellate) it would appear that it contains a substance analogous to adrenalin.—T. C. B.

The influence of pregnancy and lactation on the weight of adrenal glands in the albino rat. Donaldson (J. C.), *Am. J. Physiol. (Balt.)*, 1924, 68, 517-522.

There is no increase in weight of the adrenals in normal rats during pregnancy and lactation, but in unmated pathological rats the adrenals are increased in weight and the weight is further increased during pregnancy.—T. C. B.

Influence of adrenalin on the concentration of urea in the blood (*Influence de l'adrénaline sur la concentration uréique du sang*). Du Bois (C.) & Polonovski (M.), *Compt. rend. Soc. de biol. (Par.)*, 1924, 91, 293-295.

Under the influence of adrenalin the concentration of urea in the blood is augmented when compared with controls without adrenalin. The mechanism by which this occurs will be discussed in a later paper.—T. C. B.

**Suprarenal enlargement under heavy dosage with insulin.** Riddle (O.), Honeywell (H. E.) & Fisher (W. S.), *Am. J. Physiol.* (Balt.), 1924, **68**, 461-476.

Single heavy doses of insulin or, repeated less heavy doses, results in suprarenal enlargement. There is some evidence that repeated heavy doses is followed in a few days by a lessened capacity of these doses of insulin to maintain the blood sugar at a low level. This seems to be coincident with the appearance of enlargement of the suprarenals.—T. C. B.

**The effect of adrenalin upon the patellar tendon reflex.** Tuttle (W.), *Am. J. Physiol.* (Balt.), 1924, **69**, 446-447.

Adrenalin chloride was given intramuscularly to 9 human subjects. In 6 cases there was no effect; in 3 cases there was augmentation due, it is suggested, to a direct effect on the sympathetic fibers to the muscle.—T. C. B.

**Pigmentation of the skin (Addison's disease) associated with lymphosarcoma involving particularly the retroperitoneal lymph nodes of the solar plexus region.** Warthin (A. S.), Crane (A. W.) & Jackson (J. B.), *Arch. Dermat. & Syph.* (Chicago), 1924, **10**, 139-162.

The patient was seen during the six and a half years of the course of the disease by many physicians, and was presented at several scientific societies. The clinical diagnoses varied from "hyperpigmentation" to acanthosis nigricans. The patient was a teacher, 37 years old, whose family history was negative. His personal history, up to the onset of this disease, was negative except, possibly, for an injury to the back at the age of 23 in a game of football. The present trouble began in July, 1916, with pain in the region of the appendix, accompanied by nausea, vomiting and diarrhea. In the spring of 1919 he consulted a physician on account of an increasing pigmentation of the skin. In the autumn of the same year he showed some anemia. Two years later traces of albumin and a few hyaline casts appeared in his urine. In the summer of 1922, with strenuous outdoor exercises and study at night, he began to have headaches. A little later he developed difficulty in speaking, and, after a fall into the water when he became thoroughly chilled, he was found the following morning semicomatose, with paralysis of the right side of the face and the right arm and hand. This condition gradually improved, but he continued to have attacks of syncope with nausea and increasing disability of the right hand and the face. On September 10th, 1922, enlargement of the superficial lymph glands was first noticed. The pigmentation was more pronounced. No palpable masses could be felt in the abdomen. Systolic blood pressure was 120; diastolic, 70. The hemoglobin (75%) and the red cell count (3,780,000) were approximately the same as

three years previously. The leucocyte count was 3,000. Some of the lymph glands removed from the right groin were diagnosed by Warthin as generalized lymphosarcoma, probably most marked in the retroperitoneal group, involving solar and suprarenal plexus. He was then given intensive deep roentgen-ray therapy, 10 treatments in 10 days. There was no change in the pigmentation and no reduction in the size of the lymph glands. He developed various symptoms ascribed in part to roentgen-ray sickness and in part to taking cold. The treatments were discontinued. He died November 22d, 1922, 10 days after the last roentgen-ray treatment. His death occurred more than 6 years after the beginning of the abdominal symptoms and more than 4 years after the onset of pigmentation of the skin. The findings at autopsy and on microscopic examination of the tissues are given in great detail. The important features of the anatomical diagnosis were as follows: Generalized aleukemic lymphoblastoma (lymphosarcoma), primary in the retroperitoneal lymph nodes; pressure atrophy of the solar plexus and adrenals; extreme melanoderma (atypical Addison); melanosis of the cutaneous surfaces of the superficial lymph nodes; roentgen-ray necroses in the lymph nodes, liver and gastro-intestinal tract; phagocytosis of chromatin particles by the reticulo-endothelial system; terminal hemorrhagic necrotic pneumonia; fibrinopurulent pleuritis; chronic parenchymatous nephritis (secondary contracted kidney); arteriosclerosis, most marked in the branches of the left middle cerebral artery; multiple anemic infarctions of the left cerebral hemisphere with liquefaction; atrophy, passive congestion and parenchymatous degeneration of all organs; thymicolymphatic constitution, and aspermatogenesis. In the opinion of the authors there is no reason why the condition should not be classed as Addison's disease. This patient showed the characteristic constitutional anomaly of the thymicolymphatic constitution, "which is apparently always associated with Addison's disease." A pluriglandular endocrinopathy was also shown by changes in the thyroid, parathyroids and hypophysis. The pigmentation in the skin and superficial lymph nodes was said to be due to the presence of melanin. The authors believe that the pigment was chiefly if not wholly the product of specialized reticuloendothelial cells lying in or on the walls of the capillaries of the papillary layer of the corium. "In conclusion, the case here studied is one of Addison's disease, due to pressure atrophy of the chromaffinic tissues of the abdominal sympathetic and suprarenals produced by a generalized aleukemic lymphoblastoma primary in the retroperitoneal nodes."—J. P. S.

The influence of adrenalin on the phosphorus and the calcium of the blood (*L'influence de l'adrénaline sur la phosphatémie et la calcémie*). Woringer (P.), *Compt. rend. Soc. de biol. (Par.)*, 1924, 91, 588-590.



Adrenalin seems to have an elective action on the blood phosphate. There is an initial fall, followed by a rise above normal which lasts for some time. There is little variation in the calcium due to adrenalin.—T. C. B.

**Obesity and its treatment.** Anders (J. M.), *Atlantic M. J.* (Harrisburg), 1924, 27, 498-501.

This is a brief, general review of the subject. Though the thyroid, pituitary and gonads are frequently involved in simple obesity the endocrine factors are of slight etiological importance. It is pointed out that in the ordinary form of obesity the basal metabolism is practically normal. Thyroid opotherapy should not be resorted to unless the patient is anemic and flabby, presenting a "myxedematoid" variety of the disease, and in those instances of adiposity among females in whom menstruation is scanty and irregular. Ovarian preparations are useful in the obesity of menopause. Endocrine opotherapy, especially thyroid, should of course be employed with great caution.—I. B.

**On the glycogenic function of the liver and its endocrine control.** Cramer (W.), *Brit. J. Exper. Path.* (Lond.), 1924, 5, 128-140.

The glycogen of the liver is not a reserve store of excess carbohydrate, but a product of secretion of the liver-cells—an "internal secretion" of the liver as defined by Claude Bernard. The glycogenic function of the liver is an autonomous secretory function, by which the liver forms carbohydrate in the form of glycogen independently of any supply of preformed carbohydrate in the food and secretes it into the blood in the form of glucose. By means of this function the level of the blood sugar is prevented from falling below a fixed minimal level, because the liver automatically secretes sugar when this level is reached. Another aspect of this glycogenic function is that by its stimulation more carbohydrate is formed and more glucose is secreted into the blood. The specific protein-sparing action of carbohydrates in the general metabolism is due to carbohydrate protecting protein from being used by the liver for the formation of glycogen. The glycogenic function is inhibited by the pancreatic hormone. It is stimulated by the sympathetic system and by the thyroid and adrenal hormones. This stimulation and inhibition affects both the formation of carbohydrate by the liver and the secretion of glucose into the blood. The antagonism between these two groups of hormones is restricted to the glycogenic function of the liver and not to the carbohydrate metabolism of individual cells or organs; in fact, both groups of hormones increase the consumption of carbohydrates by individual organs, although in different ways. The inhibition of the glycogenic function of the liver is an essential factor in bringing about the hypoglycemia after insulin. When the inhibiting influence of the pancreatic hormone is absent,

as in pancreas diabetes, the glycogenic function of the liver becomes hyperactive. The hyperglycemia of diabetes mellitus is the result not only of an impaired oxidation of glucose by the cells, but also of an increased formation of carbohydrate by the liver, and an increased secretion of glucose into the blood. The therapeutic effect of insulin in diabetes mellitus is directed not only towards improving the oxidation of carbohydrates by the cells, but also towards inhibiting the hyperactivity of the glycogenic function of the liver. Stimulation of the glycogenic function by the thyroid and adrenal hormones leads in a normal organism to increased oxidation of carbohydrates, increased formation of carbohydrates from proteins, increased heat production and increased nitrogen excretion. It occurs in such conditions as experimental hyperthyroidism, Graves' disease, exposure to cold and sympathetic fever.—Author's Summary.

Endocrinology and pediatrics. Draper (G.), Med. Clin. N. Am. (Phila.), 1924, 8, 55-70.

A general résumé of the known and implied facts pertaining to the pathology of the internal secretions in early life. The author reviews the literature on the pituitary gland, in which the various syndromes of hypophyseal disorder are discussed. In the author's experience, skeletal measurements of children are of doubtful value because of the growth factor; it is probably not justifiable to compare children with a year or six months age difference as we compare full grown adults, belonging to a given disease group. Moreover, fat children have shown an average skeletal growth in proportion to their age, and their disturbance of form has been due entirely to excess fat deposition. All male subjects, in the experience of the author, have shown incomplete development of the gonads. With regard to infantilism, the outstanding feature of the Lorain-Levi type, aside from the fact of small size, is the continuance of the open epiphyses. The fact that in some of these instances undernourishment plays its part must not be forgotten. In a case of sexual precocity studied by the author, in which it was suspected that tumors of the pineal gland existed, operation failed to reveal any neoplasm either of the hypophysis or of the pineal. The difficulties of the diagnostician are increased when confronted with tumors of the pituitary, not only in instances of acromegaly or gigantism, but also with infantilism of the Lorain type and adiposity and gonadal atrophy of the Frölich type. Again, sex precocity in the male has been found with tumors in the pineal, and in Cushing's case, without evidence of intracerebral tumor. Many other instances of confusing data might be cited, calling into question whether recognized clinical syndromes are really due to faulty glandular balance. Why does similar pathology of the glands produce different symptom complexes in different individuals, and what are the limits

of the activities of the glands of internal secretion? We are moving into an uncharted sea, and it is necessary to proceed with the same respect for observed facts and their co-relation that the mariner does under such conditions.—I. B.

**Influence of internal secretions on growth and function.** Lawrence (C. H.), Boston M. & S. J., 1924, 191, 157-161.

Our knowledge of endocrine disorders is based on cases in which the dysfunction has produced extensive alterations in the individual. Early diagnosis may make it possible to prevent such changes, but must be based on a knowledge of the less obvious and earlier signs of endocrine disturbance. The author notes what signs appear early in the disturbances of the different individual glands. The author believes that accurate diagnosis of disorders of internal secretion can be made in the majority of cases by combining certain vital function tests with carefully obtained history and a thorough physical examination. He states that pluriglandular syndromes form but a small fraction of endocrine disorders, and therefore that the use of pluriglandular preparations, like polypharmacy in general, is illogical and useless. Increase of our knowledge of the endocrine functions depends upon the collection of facts obtained by objectively controlled clinical studies.—J. C. D.

**Action of the endocrine glands and their extracts on the development of plants** (*Action des glandes à sécrétion interne et de leurs extraits sur le développement des plantes*). Rebello (S.), *Compt. rend. Soc. de biol. (Par.)*, 1924, 90, 1095-1097.

Hyacinth bulbs were chosen as experimental material and grown in simple contact with water, to which various endocrine substances were added. Bulbs grown in solutions containing powdered thyroid, or thyroproteins, or pituitrin, showed an acceleration of growth, both tops and roots. On the other hand, contact with fresh organs (thyroid, muscle, thymus) caused inhibition of growth.—T. C. B.

**Diagnosis of endocrine disorders.** Rowe (A. W.), Boston M. & S. J., 1924, 191, 151-157.

The author summarizes this paper as follows: "1. An objective method for the diagnosis of endocrine disorders is briefly outlined. 2. The results obtained in a series of 160 cases are statistically presented. 3. The thyroid influences the basal metabolic rate profoundly, the pituitary, gonad and adrenal only slightly, but in the same sense. 4. Endocrine disorders tend to lower blood pressure. 5. Vital capacities are least influenced by pituitary disease; most by thyroid. 6. The Dreyer standards based on chest and weight measurements are criticized adversely. 7. Thyroid cases apparently show lowered urine elimination, which is duplicated by the phenolsulphonephthalein test. With this latter, the adrenal cases show the

same tendency. 8. An appreciable number of pituitary cases give a positive response to Ehrlich's 'Urobilinogen' test. 9. Endocrine cases in general show a marked increase in the undetermined N<sub>2</sub> fraction in the urine. 10. The blood uric acid is raised above normal in many pituitary cases without an equivalent increase in the other nitrogenous constituents. 11. Blood sugar levels are usually low in endocrine conditions. 12. Over 20% of all cases in this series show a low-grade mellituria. Only two of these were diabetics. Among the non-endocrine cases, syphilis and lesions of the central nervous system seemed to be predominant causes. 13. The majority of the endocrine cases show a marked lymphocytosis and an appreciable number demonstrate a mild eosinophilia. The gonad cases are an unique exception, their percentages approximating those of the non-endocrine cases. 14. The sex difference observed in the threshold of tolerance for galactose is noted and an explanation based upon diverse mammary function is offered. 15. The pituitary exercises a profound influence on the carbohydrate metabolism; the thyroid has slight effect and one in the same sense; the gonad has an intermediate effect, exercised in the opposite sense with women, and producing no change from the normal with men."—J. C. D.

**The induction of a sexually mature condition in immature females by injection of the ovarian follicular hormone.** Allen (E.) & Doisy (E. A.), *Am. J. Physiol. (Balt.)*, 1924, 69, 577-599.

Four to six injections of ovarian follicular hormone may induce a sexually mature condition of the genital tract in two or three days, as early as 26 days of age. It is suggested that the follicular hormone is responsible for the attainment of sexual maturity in the female.—T. C. B.

**Further results with ovarian implantation.** Estes (W. L.), *J. Am. M. Ass. (Chicago)*, 1924, 83, 674-777.

Ninety-five cases form the basis of this paper. Conservation of the ovary was practiced in these cases. The tube and ovary of the side opposite the implantation are first removed. The tube of the implanted side is then removed, together with enough of the horn of the uterus, at the tubal attachment, to leave a raw area the size of the cut surface of the ovary. A longitudinal slice is then taken through the full diameter of the ovary, removing usually about one-quarter of it from the surface opposite its ligament and mesentery. The amount of ovary removed depends on the amount of cystic degeneration or inflammation that may be present. As high as seven-eighths of the ovary has been removed and the remainder implanted. The cut surface of the ovary is then turned over on the denuded area of the uterine horn and sutured in place by a continuous catgut suture, beginning at the inferior margin and approximating the complete circumference of the ovarian and uterine wounds. The

operation was performed on patients whose ages ranged from 16 to 41. It was usually considered for young women below 30 because in the older women there is less desire for and less likelihood of pregnancy occurring. A very edematous uterus, which is evidently involved in the inflammation, is considered a contraindication. No plastic operation is attempted if there is present a large pyosalpinx or pelvic abscesses. Ninety-three cases have been investigated, but of 45 patients traced four became pregnant. Two women had miscarriages at about three months. Menstruation was regular, with the usual duration in thirty-three, irregular in five, and either profuse or scanty and painful; in three cases the report was insufficient for accurate deductions; only four patients failed to menstruate at 23, 28, 31 and 37 years, respectively. In two of these, only a very small portion of the ovary was saved. There was almost always some gain in weight, usually from 15 to 75 pounds (7 to 34 kg.). Normal menopause, following the implantation, after menstruation for seven or more years, occurred in eight patients; in one, at the age of 33; in the others, at from 41 to 47 years. Fifteen complained of some pain, usually with the menses, either headache, backache, or pain in the same side as the implanted ovary. One woman had, with menstruation, rather severe pain in her breasts, and backache. Twenty-three, or about 50%, of the patients acknowledged that they often felt nervous. One believed she was less nervous following the operation. One woman, about a year after the operation, developed symptoms of hyperthyroidism.—Courtesy A. M. A.

**Antagonism of the sexual glands in experimental hermaphroditism** (*Le probleme de l'antagonisme des glandes sexuelles dans l'hermaphroditisme expérimental*). Lipschütz (A.) & Voss (H. E. V.), *Compt. rend. Soc. de biol. (Par.)*, 1924, 90, 1041-1043.

From previous experiments with intrarenal ovarian transplantation with reduction of the testicular mass, as well as experiments here described, it is concluded that the testicles in situ influence negatively the ovarian grafts as far as their hormonal action is concerned.—T. C. B.

**Experimental hermaphroditism** (*Hermaphroditisme expérimental causé par transplantation ovarienne intrarenale avec reduction de la masse testiculaire*). Lipschütz (A.) & Voss (H. E. V.), *Compt. rend. Soc. de biol. (Par.)*, 1924, 90, 1139-1141.

Of 17 guinea pigs in which as much as two ovaries had been transplanted by the intrarenal method, and the mass of the testicles considerably reduced, 16 showed a maximal development of feminine characters after a short latent period. The greater number of animals retained their masculine characters. The endocrine functions of the testicular fragments was not inhibited, even by two ovaries in maximal endocrine function.—T. C. B.

Experimental hermaphroditism on quantitative lines (intratesticular ovarian transplantation by the method of Sand). Lipschütz (A.), Krause (W.) & Voss (H. E. V.), *J. Physiol. (Lond.)*, 1924, 58, 461-465.

The statements of Steinach and of Sand that the simultaneous development of male and female sex characters can be conditioned by the presence of testicle and ovary in the same organism is confirmed quantitatively.—T. C. B.

Fate and function of the ovaries after hysterectomy. Maxwell (Alice F.), *J. Am. M. Ass. (Chicago)*, 1924, 83, 662-666.

The report consists of an analysis of the surgical menopause as it occurred in women with and without ovarian tissue. The frequency, severity, time of onset and duration of ablation symptoms have been studied and contrasted with similar disturbances of the natural menopause. Factors that might tend to modify these symptoms have been reviewed and grouped according to the age of the patient, her general condition before operation, the pelvic pathologic condition and the type of ovaries that were retained. The value of the conserved glands has been balanced against their tendency to degeneration. To complete the study, results with ovarian therapy have been included. The material consists of 500 cases of hysterectomy, followed from one to eight years. If the normal menopause is accepted as a control, this analysis indicates that: 1, the frequency of vasomotor symptoms after hysterectomy is increased when both ovaries are removed; 2, the frequency of symptoms with conserved ovaries after hysterectomy compares favorably with that of the normal menopause; 3, severe vasomotor symptoms are more common without than with ovaries; 4, the onset of delayed symptoms indicates that a definite number of conserved ovaries will atrophy within a year after operation; 5, the average duration of symptoms of the normal and surgical menopause is about two and one-half years; 6, women with low hemoglobin are more likely to develop post-operative disturbances; 7, the frequency of symptoms depends in large measure on the type of tissue retained; 8, retained healthy ovaries are not susceptible to degeneration.

—Courtesy A. M. A.

Hyperglycemia and glycosuria in acromegaly. Ellis (A. W. M.), *Lancet (Lond.)*, 1924, i, 1200-1203.

A case of glycosuria occurring in an acromegalic patient showed the following points of especial interest: (1) severe hyperglycemia, the blood sugar on admission being 0.43%; (2) the successful accomplishment, after adequate dieting, of a major operation of prolonged nature, and the occurrence of only transient postoperative glycosuria; (3) the disappearance of glycosuria and hyperglycemia following hypophysectomy and, although diminished carbohydrate

tolerance is still present, the absence of glycosuria 3 years after the operation; (4) histologic evidence suggesting the origin of the tumor in the pars intermedia; (5) the occurrence of a tumor of the carotid body. The suggestion is advanced by Ellis that the glycosuria of acromegaly is due to an increased activity of the hypophysis, probably the pars intermedia, with a resulting interference with the normal action of insulin on carbohydrate metabolism.—J. Am. M. Ass., 83, 389.

**Pathologic changes in the pituitary body in wild animals.** Fox (H.), Rep. of the Lab. & Mus. of Compar. Pathol. of the Zool. Soc. of Phila., 1924, p. 23.

"Knowledge of this structure (pituitary body) is meager despite the intensive work expended upon its study in recent years, so that even in the absence of conclusions of any sort observations upon its diseases are worthy of record." The following 3 cases are briefly described and illustrated. (1) A female Indian Buffalo (*Bos bubalis*) had borne 3 young, was known to be drooping for a few days, and died from a very large hemorrhage from an erosion of the basilar part of the occiput caused by a large blood-red soft tumor of the pituitary body which had eaten away the sella turcica, pushed the optic nerve forward and extended back beyond the crura almost to the foramen magnum. The mass measured 4.5 x 4 x 2.5 cm. Sections of the tumor showed "three kinds of tissue—a finely fibrillar or homogeneous background or framework in which lie dilated blood spaces containing whole or degenerated blood, or cellular groups in strands and in acinus formation, being almost invariably surrounded by a condensation of connective tissue sufficient to be called a basement membrane." There had been much hemorrhage into the growth. "Because of the adenomatoid character, the papillomatoid growth in places, the cysts, this is probably to be called a struma with adenomatoid parts and much hemorrhage." (2) "The pituitary body of a common opossum (*Didelphys virginiana*) was deeply injected and soft, measuring 10 x 8 x 5 mm. This is considered large for this animal. It has not been sufficiently studied to report upon it." (3) A springbok (*Gazella anchore*) died from a variety of causes, caries of the jaw bone from carious teeth, ulcerative gastritis, parasitic enteritis—"and showed a pituitary body deep red, soft irregularly outlined character, varying around 1.5 cm. in different dimensions. There is nothing in the history that suggests intracranial disease. The microscopic picture is of a compact tissue with deeply stained cells in small packets, no lumen suggesting an acinus. The size and color indicate its gross abnormality.

—J. P. S.

**A case of diabetes insipidus with infantilism.** Gask (G. E.), Proc. Roy. Soc. Med. (Lond.), 1924, 17, 31-32 (Clin. Sect.).

The patient is a male 29 years old who, while in the military service of 1917, contracted malaria. This was followed by symptoms of diabetes insipidus, and within a short time also by hypoplasia of the gonads, a sparseness of the hair on the face, dry skin, loss in weight, a more youthful appearance, and fatigability. X-ray examination of the sella was negative. Hypodermic injections of pituitrin improved the polyuria.—I. B.

Cutaneous and genital modifications produced in the toad by extirpation of the hypophysis or by lesion of the brain (*Modifications cutanées et génitales produits chez le crapaud par l'extirpation de l'hypophyse ou par lésion du cerveau*). Giusti (L.) & Houssay (B. A.), *Compt. rend. Soc. de biol. (Par.)*, 1924, 91, 313-317.

Total extirpation of the hypophysis in the toad induces a considerable mortality (85 per cent), attenuation of the pigment of the skin, atrophy of the testicles, abortion in adult females, and the development of a black cuticle. Injury to the tubo-infundibular region leads to a passing darkening of the skin, no testicular atrophy, a black cuticle, and abortion.—T. C. B.

*Diabetes insipidus*. Hamilton (W. F.), *Med. Clin. N. Am. (Phila.)*, 1924, 7, 1971-1982.

A general review of the subject with 3 illustrative case histories. With regard to the prognosis, the syndrome is not incompatible with long life unless there exists an organic lesion of the pituitary or at the base of the brain. Lumbar puncture, antiluetic treatment, a diet low in protein and salt, valerian, and the hypodermic or intranasal administration of pituitrin are useful therapeutic measures.—I. B.

The vasomotor activity of pituitary extracts throughout the vertebrate series. Hogben (L. T.) & Schlapp (W.), *Quart. J. Exper. Physiol. (Lond.)*, 1924, 14, 229-258.

Whereas adrenalin produces a rise in blood pressure in all four classes of air-breathing vertebrates, pituitary extracts which had no depressor action in the mammal consistently causes depression in birds and reptiles. It is concluded that the pronounced depressor action of small doses of pituitary extract on the avine circulation is not due to the substance causing depression in mammals.—T. C. B.

Antagonistic action of extracts of the anterior and posterior lobes of the hypophysis on the coagulation of blood (*A propos de l'action antagoniste des extraits des lobes antérieur et postérieur de l'hypophyse sur la coagulation du sang*). La Barre (J.), *Compt. rend. Soc. de biol. (Par.)*, 1924, 91, 601-604.

Various experiments seem to show that extracts of the posterior lobe *in vitro* are incapable of inducing coagulation, but may acceler-



ate the mechanism for the formation of thrombin and fibrin. Extracts of the anterior lobe retard coagulation, probably by the presence of cholin.—T. C. B.

**Pituitary dysfunction.** Mackay (F. H.), *Med. Clin. N. Am. (Phila.)*, 1924, 7, 1789-1804.

A review of the subject with 5 illustrative case histories. Aside from a degree of benefit obtained in some cases of pituitary headache, pituitary feeding, in the author's experience, has been found generally incapable of alleviating hypophyseal syndromes.—I. B.

**Metastatic carcinoma of the pituitary gland and diabetes insipidus.** Piney (A.) & Coats (Ida), *J. Path. & Bacteriol. (Edinb.)*, 1924, 27, 211-215.

The patient was a woman 40 years old who, on account of carcinoma, had had the right mammary gland removed 23 months before death. "Whilst still in fair health" she consulted a physician "who found few physical signs other than slight enlargement of the cervical glands on the left side and some mental hebetude, and elicited a history of great polyuria." Two weeks later the patient was admitted to the hospital in a state of coma and died "a few days later." The amount of urine passed daily while in the hospital exceeded 5 liters. At autopsy metastases were found in the lower cervical glands on the left side, in the mediastinal fat, in the left suprarenal, and in many parts of the cerebrum and cerebellum. The pituitary was slightly enlarged and the posterior lobe projected backward. On microscopic examination the posterior lobe was found to be completely replaced by carcinoma cells. Only one vesicle containing colloid could be found, and this appeared to be the only portion of the pars intermedia which was not destroyed by the cancerous growth. The authors believe that this case furnishes evidence in favor of the conception of the causation of diabetes insipidus by secretion of the pars anterior.—J. P. S.

**Studies in diabetes insipidus.** Rowntree (L. G.), *J. Am. M. Ass. (Chicago)*, 1924, 83, 399-405.

Fifty-six cases of diabetes insipidus are reviewed. The average age at onset was less than 30 years. Cerebral and pituitary lesions, injuries of the head, and fractures, particularly of the base of the skull, bear a striking and intimate relationship. The condition arises, occasionally, during convalescence from acute febrile diseases. In cases of the secondary type, lesions of the hypophysis or of its immediate neighborhood play a leading part. Benign or malignant neoplasms, in some instances primary, in other metastatic in origin, are responsible in most of these cases. A history of removal of a malignant tumor elsewhere in the body, with the subsequent development of polyuria within a few months or years, is

not uncommon. Syphilis, congenital or acquired, is also an important etiologic factor. Two types of diabetes insipidus are usually recognized: the primary or idiopathic, and secondary or symptomatic. Thirty-six of these cases were primary. Of the secondary group, 9 cases were secondary to cerebral and pituitary neoplasm, 7 to syphilis, and two each to trauma and encephalitis. The cardinal symptoms of diabetes insipidus are thirst, polyuria and polydypsia. These were present in all cases. Cerebral manifestations occur in a considerable number of cases, and usually indicate the secondary character of the disease. Evidence of disturbed pituitary function is encountered frequently. Two cases, secondary to encephalitis, were of especial interest, as they revealed, besides the diabetes insipidus, definite clinical evidence of Parkinson's disease. The course of the disease is largely dependent on the nature of the underlying process. In about one-half of the cases, traces of albumin were found, and not infrequently larger amounts, constituting a definite, unmistakable albuminuria. Casts were consistently absent. Occasionally the urine contained a few red and white blood cells. Glycosuria was found in one case, the condition having been previously diagnosed diabetes mellitus. The concentrating capacity of the kidney was uniformly diminished. As a rule, the blood is normal in regard to the percentage of hemoglobin and the number of erythrocytes and leukocytes. In 43 cases, roentgenograms of the skull were made. Definite enlargement of the sella was found in 4 cases; changes in the clinoid processes with normal sized sella in 3, and bridging of the sella in 2. A comminuted fracture in the parietal area was also present in one case. In only one case in the idiopathic group was an abnormality found in the sella; this was an instance of bridging. The basal metabolism was determined in 23 cases, and was on an average approximately 15% lower in the secondary types. In only one of the secondary cases was the basal metabolism definitely increased above the normal, and this was in a patient with acromegaly who had had partial thyroidectomy 2 years before, the condition suggesting adenoma. Positive objective neurologic findings appear only in cases of the secondary type, and the findings are those usually associated with cerebral or pituitary neoplasm, syphilis of the central nervous system, trauma or encephalitis. Our experience indicates that the course of the disease depends on the underlying pathologic condition, rather than on the disease per se. In estimating the effects of treatment in cases of diabetes insipidus, it is necessary to permit the patient to take water ad libitum. Consistently good results were obtained only from the frequent subcutaneous administration of the extract of the posterior lobe of the pituitary. However, in a few cases, effects of considerable value were obtained at times from its intranasal use as a spray, instilled into the nostril by a medicine dropper, or applied on a pledget of cotton. Similarly, rectal administration was sometimes helpful, but

only for short periods, usually for from 2 to 4 hours. Oral administration, in the form of tablets or liquid, was extremely disappointing. No serious untoward effects from organotherapy have been encountered in any of the cases in the series. Spinal puncture has been tried in 19 cases without untoward effects, other than the headache that incidentally follows this procedure at times. In not a single instance has it had an effect comparable in any way to some of the results cited in the literature. Treatment for syphilis has been carried out vigorously in several of our cases without any recognizable effect on the diabetes insipidus, except, perhaps, in one instance. In cases secondary to neoplasm, operation should be considered on its own merits and without reference to the existence of diabetes insipidus.—Courtesy A. M. A.

**The lingual administration of insulin** (*L'administration perlinguale de l'insuline*). Blum (L.), *Compt. rend. Soc. de biol. (Par.)*, 1924, **91**, 199-201.

The mucous membrane of the tongue is absorbent, and if a very soluble preparation of insulin (the hydrochlorate prepared by Dudley) is used, the blood sugar falls. Two to three times the amount used subcutaneously is necessary, and its action is less constant.—T. C. B.

**Studies in tissue respiration. Method of action of insulin** (*Studien über Gewebsatmung. Zur Kenntnis der Wirkungsweise des Insulins.*) Büchner (S.) & Grafe (E.), *Deutsches Arch. f. klin. Med. (Leipz.)*, 1924, **144**, 67-85.

The respiratory exchange of thin slices of various tissues in an oxygenated Ringer's solution containing glucose was estimated by means of a Barcroft manometer. The oxygen consumption per gramme of dried tissue varied within narrow limits whatever the organ utilized. The addition of insulin to the Ringer's solution leads to a great increase in oxygen consumption and usually raises the respiratory quotient. The increased oxygen consumption was noted in kidney, liver, heart, muscle, spleen, etc. Insulin acts, therefore, on all the organs of the body, and its action is not limited to the liver.—*Med. Sc.*, **10**, 411.

**Contributions to the physiology of the stomach. Influence of experimental changes in blood sugar level on gastric hunger contraction.** Bulatao (E.) & Carlson (A. J.), *Am. J. Physiol. (Balt.)*, 1924, **69**, 107-115.

In conditions found to increase gastric hunger contractions there is either a decrease in tissue glycogen or an inability of the tissue to burn sugar. In man insulin hypoglycemia is accompanied by increased hunger. It is possible, therefore, that the availability of carbohydrates for tissue utilization may be a factor in the genesis

or intensity of hunger contractions. If this hypothesis is correct, experimental hyperglycemia should inhibit hunger contractions, and experimental hypoglycemia should lead to the onset, or increase the intensity of gastric hunger contractions. Also, in depancreatized animals increase of the blood sugar level should not inhibit hunger contractions, but the administration of insulin should cause a temporary depression of the contractions followed by augmentation when a certain degree of hypoglycemia was reached. Experiments were made on dogs, the hunger contractions being recorded by the well-known method of Carlson, and sugar determinations by the method of Folin and Wu. The results show that intravenous injections of glucose inhibit contractions; insulin hypoglycemia augments hunger contractions when the sugar reaches 0.07-0.08 per cent. Glucose inhibits the gastric tetany of hypoglycemia. In diabetic dogs insulin produces a primary depression followed by increased tonus and contractions. Injections of glucose do not inhibit in diabetic dogs, except when hypoglycemia and tetany (gastric) are induced by insulin.—T. C. B.

The effect of insulin on the respiratory exchange of normal animals.

Dickson (B. R.), Eadie (G. S.), Macleod (J. J. R.), & Pember (F. R.), *Quart. J. Exper. Physiol.* (Lond.), 1924, 14, 123-149.

The results of many experiments on dogs and rabbits are not the same. In dogs there was a marked increase in respiratory volume after the blood sugar had completed the initial fall, the increase often associated with hyperexcitability, and a corresponding increase in oxygen consumption and in energy metabolism. The R. Q. was increased. In rabbits there was no increase in respiratory volume and only a doubtful increase in oxygen consumption, at least prior to the onset of convulsions.—T. C. B.

Observations on the circulation during hypoglycemia from large doses of insulin. Edwards (D. J.) & Page (I. H.), *Am. J. Physiol.* (Balt.), 1924, 69, 177-189.

Dogs were used rendered analgesic by iso-amyl-ethyl-barbituric acid which has practically no effect on the circulation nor on the blood sugar. A single large dose of insulin (25 to 35 units per kilo) brought the sugar level down to 0.05 to 0.012. There was a moderate decline of mean blood pressure during the first two hours, followed sometimes by recovery, sometimes by a rapid decline. There was no change in peripheral resistance. The heart rate was increased. There was a rapid decrease of the dynamic capacity of the heart; a slight lengthening of the isometric phase and a shortening of the period of rising pressure and of the systolic ejection time.—T. C. B.

**Diabetes refractory to insulin.** Falta (W.), *Klin. Wchnschr.* (Berl.), 1924, 3, 1315-1317.

Falta reports on a case of diabetes which was practically refractory to insulin. Intravenous injections were followed by an increase in blood sugar after a slight and short lowering. The patient was corpulent. The sella turcica was small, and the basal metabolism minus 17%. The author believes that the patient has sufficient insulin but that it is prevented from action.—*J. Am. M. Ass.*, 83, 651.

**A case of diabetes mellitus complicated by pregnancy, treated with insulin.** Graham (G.), *Proc. Roy. Soc. Med.* (Lond.), 1924, 17, 102-104 (Sect. Obst. & Gyn.).

The patient described was 34 years old and already had one child. She developed diabetes mellitus of average severity, and after 3 weeks of insulin treatment she became pregnant. The diabetes was aggravated by this status, but despite this, and an incidental attack of influenza, she was finally delivered of a healthy child. The subsequent progress of the patient was more favorable than before.—I. B.

**Lipoids in 1000 diabetic bloods, with special reference to prognosis.** Gray (H.), *Am. J. M. Sc.* (Phila.), 1924, 168, 35-46.

The patients in this series who lived 2 years after coming under observation had blood fats averaging less than 1 gm. per 100 cc. When the fat exceeded 2 gm. per 100 cc. the patient lived less than 2 years in 86% of the cases. The author believes that his data "demonstrate the rule that progressively each group with a higher blood fat level (or similarly with higher cholesterol) is characterized by a distinctly shorter life expectancy." Underweight diabetics, that is, the severe cases of denutrition (10% below the standard) showed blood fats 40% higher than the fat diabetics, the mild cases. "Blood sugar parallels blood fat more in averages than in individual cases." Blood fat analyses are believed to be a material aid in the diagnosis, and especially in the prognosis of diabetes mellitus.  
—J. P. S.

**Hyperinsulinism and dysinsulinism.** Harris (S.), *J. Am. M. Ass.* (Chicago), 1924, 83, 729-733.

Harris describes hyperinsulinism as a condition, perhaps a disease entity, with definite symptoms; i. e., those described as being due to hypoglycemia. It seems probable that one of the causes of hyperinsulinism is the excessive ingestion of glucose-forming foods and that, as the result of overactivity induced by overeating, the islands of Langerhans become exhausted and hypo-insulinism (diabetes) follows. It is possible that the hunger incident to hyper-

insulinism may be a cause of overeating, and, therefore, the obesity that so often precedes diabetes. It seems probable that dysinsulinism, either an increase or a decrease in the secretion of insulin, may follow infection or trauma of the pancreas. Since excessive hunger is a symptom of hypoglycemia, it may be that normal hunger is the call for glucose, and that it may be in part or wholly of pancreatic origin and not entirely an expression of an empty stomach. It is also possible that, associated with ulcer of the stomach or duodenum, there may be a coexisting disorder of the pancreas, and that the frequent feedings which give relief in ulcer may do so by supplying the glucose to meet the needs of overfunctioning islands of Langerhans. In one case of ulcer, we found a low blood sugar. Since blood pressure readings have been low in all except two of the nondiabetic patients who have had symptoms of hypoglycemia, it seems possible that hypo-adrenalism may be associated with hyperinsulinism. It also seems probable that secretory disorders of the islands of Langerhans may be associated with dysfunctions of the thyroid, the pituitary bodies and other organs of internal secretion. Fractional tests of gastric secretions after the Ewald meal have been made in several nondiabetic patients having symptoms of hyperinsulinism, with variable results, so that there is no apparent relation of secretory disorders of the stomach to pancreatic dysfunction. No studies of the external secretion of the pancreas were made in these cases. It seems probable, however, that since a chronic pancreatitis is probably a cause of dysinsulinism, the glands secreting trypsin, amylase and steapsin are often involved, with either increased or decreased function. Five cases are reported.—Courtesy A. M. A.

**The sugar of arterial and venous blood during the action of insulin.**

Hepburn (J.), Litchford (H. K.), McCormick (N. A.) & Macleod (J. J. R.), *Am. J. Physiol. (Balt.)*, 1924, 69, 555-567.

Increased disappearance of sugar from blood to muscles under the influence of insulin could not be demonstrated. Under the same conditions there is no increased disappearance of sugar in the liver. Insulin is practically without hypoglycemic effect on the sugar of depancreatized dogs under ether.—T. C. B.

**Reduction of human blood sugar by means of insulin.** Kahn (S. H.), *Boston M. & S. J.*, 1924, 191, 161-167.

The study is based on 7 normal and 26 diabetic subjects. An equation was worked out so that the reduction in blood sugar in a given case could be calculated. The data on which the equation is based and tables showing its application are given. The reduction of blood sugar in normal individuals at rest per unit of insulin is strikingly similar. The blood sugar level is a factor in the amount of blood sugar reduction. The weight probably gov-

erns the duration of the effect of insulin. The variations in reduction of blood sugar in diabetics may be accounted for to a great extent by the amount of insulin used per kilo of body weight, by the blood sugar level, and the amount of available body sugar. Insulin produces a greater fall in the blood sugar of diabetic than in normal persons; the least fall in blood sugar of diabetics takes place in those whose blood sugar level approaches the normal, and may be as low as normal. The least reduction of blood sugar per unit of insulin takes place in diabetic coma, the next lowest in pre-coma cases. The power of the body to restore the alkali reserve, marked cardiac failure and toxic goiters probably influence the action of insulin.—J. C. D.

**On the use of intarvin fat—glyceryl margarate—in diabetes mellitus.** Keefer (C. S.), Perlzweig (W. A.) & McCann (W. S.), Johns Hopkins Hosp. Bull. (Balt.), 1924, 35, 265-270.

From a careful metabolic study of 4 cases the authors conclude that intarvin fat is less ketogenic than ordinary fat. The evidence regarding this interesting academic question is, however, not entirely conclusive. From a practical standpoint the use of intarvin fat in diabetes has not been found to be of any great value, because of the fact that it is intensely disagreeable to patients to whom it is given as the chief source of fat.—R. G. H.

**The pathology of the pancreas in diabetes.** Keilty (R. A.), Atlantic M. J. (Harrisburg), 1924, 27, 492-496.

In animals the islet involvement is in the nature of an exhaustion with degeneration characterized by loss of normal granules and the absorption of fluid, i. e., "hydropic" degeneration. The character of the islet involvement in human beings is more in the nature of fibrosis, atrophy, and occasionally hydropic and hyalin degeneration. The author concludes by stating that insulin will probably clear up the entire subject in the near future.—I. B.

**Action of pancreatic extracts (insulin) in the coagulation of blood** [Action des extraits pancréatiques (insuline) dans la coagulation du sang]. La Barre (J.), Compt. rend. Soc. de biol. (Par.), 1924, 91, 393-397.

Impure insulin retards or arrests coagulation in vitro, while purified insulin does not. In the present paper it is shown that the same results obtain in vivo. Insulin purified by the method of Chabanier does not retard coagulation either in vitro or in vivo. It is suggested that cholin may be the impurity causing retarded coagulation.—T. C. B.

**Xanthoma diabeticorum.** Lough (W. G.) & Killian (J. A.), Med. Clin. N. Am. (Phila.), 1924, 8, 337-345.

A complete survey of the literature by Major yielded a total of 74 cases of xanthoma diabeticorum; this series comprises a period from 1848, when the condition was first described by Gull, until 1923. The authors of this paper report an additional case. The diagnosis must be based on the characteristic skin manifestations in a diabetic subject with hypercholesterinemia. The author believes that cases of xanthoma diabeticorum without glycosuria are probably not authentic. In addition to the high cholesterol, the total lipoids are very markedly increased. The treatment of xanthoma diabeticorum is the same as the treatment of diabetes without xanthoma. There is no need for local treatment.—I. B.

Diabetes, tuberculosis and the extra-pancreatic formation of insulin (Diabète, tuberculose et formation extra-pancréatique d'insuline). Lundberg (E.), *Compt. rend. Soc. de biol. (Par.)*, 1924, **91**, 418-420.

A method is given for extracting tubercular portions of lungs and glands, which yields a substance acting like insulin, on subcutaneous injection. Convulsions occurred in 4 cases out of 6, and they disappeared immediately after injection of glucose.—T. C. B.

Insulin, carbohydrate tolerance, and weight. Mason (E. H.), *Med. Clin. N. Am. (Phila.)*, 1924, **7**, 1761-1768.

The question uppermost in the minds of clinicians working with insulin is whether through its use a definite improvement in carbohydrate tolerance can be obtained. The answer to this question depends upon the severity and duration of the illness, and the age and other factors pertaining to the patient. Mason illustrates his remarks by 7 case histories. Insulin per se will in some severe cases of diabetes increase carbohydrate tolerance. It is unwise to allow patients to gain more than their theoretic weight, as an excess is an increased burden upon pancreatic function, which would serve to lower carbohydrate tolerance.—I. B.

The influence of chloroform, ether and chloralose on the action of insulin (De l'influence du chloroforme, de l'éther et de la chloralose sur l'action de l'insuline). Mauriac (P.) & Aubertin (E.), *Compt. rend. Soc. de biol. (Par.)*, 1924, **91**, 36-37.

Experiment shows that the action of insulin is very irregular in animals submitted to the action of chloroform, ether or chloralose. This irregularity is especially marked in dogs.—T. C. B.

The influence of atropin on the action of insulin (De l'influence de l'atropine sur l'action de l'insuline). Mauriac (P.) & Aubertin (E.), *Compt. rend. Soc. de biol. (Par.)*, 1924, **91**, 38-39.

The action of atropin is somewhat similar to the anesthetics, and renders the post insulin hypoglycemia inconstant.—T. C. B.



Notes on the treatment of diabetes mellitus. Mosenthal (H. O.), Med. Clin. N. Am. (Phila.), 1924, 8, 81-101.

A discussion in which the author stresses especially the importance of a simplified, weighed dietary and the methods of insulin administration. The actual weighing of the food gives no trouble; the difficulty lies with calculation of the food ingredients necessary to make up the quantities of protein, fat and carbohydrates called for. Mosenthal details his own scheme of dietary management in diabetes mellitus, and draws the following deductions from his experience with insulin: the effect of each dose of insulin is transient, attaining its maximum in about 4 hours, then gradually ceasing to control the sugar metabolism; the acidosis is diminished in direct proportion to the glucose utilized; 1 unit of insulin will give a drop of approximately 8 mg. per 100 cc. of blood; insulin diminishes blood sugar and sets aside glycosuria by effecting an increased utilization of glucose, while starvation accomplishes this by allowing the accumulated glucose to escape in the urine; insulin brings about a storage of glycogen from glucose; smaller doses will bring about a greater digestion of starchy food per unit than larger doses; in some instances it is dangerous to advise the use of insulin even though glycosuria exists. This latter is true when the blood sugar is near a normal level in spite of the fact that glycosuria exists. The administration of insulin under such conditions may lead to hypoglycemic shock, especially in children.

—I. B.

Absorption of insulin by rectum. Peskind (S.), Rogoff (J. S.) & Stewart (G. N.), Am. J. Physiol. (Balt.), 1924, 68, 530-541.

Insulin per rectum along with blood, serum or water is absorbed and reduces blood sugar. Large doses are necessary. Insulin in NaCl solution per rectum does not induce the characteristic change in blood sugar.—T. C. B.

Insulin and diet in diabetes. Petty (O. H.), Atlantic M. J. (Harrisburg), 1924, 27, 717-722.

A review of the modern treatment of diabetes, containing the author's personal experiences with insulin and dietary management. The following points aid Petty in deciding the initial dose of insulin to be used in the beginning of treatment: (1) the amount of acidosis as evidenced by laboratory tests; (2) the stage of nutrition of the patient; (3) the height of the blood sugar; (4) the total daily caloric intake which the patient will need. Petty's custom in dividing the total daily dose is: 6 units or under, 1 injection daily; 12 to 36 units, 2 or 3 injections daily; 36 units or over, 4 injections daily. In hypoglycemic collapse, the objective findings are more important than the subjective symptoms. Nervousness, weakness, and excessive gnawing hunger are the main symp-

toms. Since these symptoms may be complained of in the most severe cases of diabetes, they are per se not important except as indications to the physician to look out for other more direct evidences of hypoglycemia, such as tremor, anxious expression, profuse perspiration, and an increase of the deep reflexes. When these signs occur, blood is immediately taken for a sugar determination, and then 15 or 20 grams of carbohydrates are administered by mouth. If the condition is not markedly improved within 30 minutes (by which time the sugar estimation should be completed), carbohydrate administration is repeated. In the event of unconsciousness and inability to swallow, 15 to 20 grams of glucose intravenously will restore the patient to consciousness and relieve all symptoms within a few minutes. In the absence of a sterile solution of glucose, a hypodermic of 1 cc. of a 1-1000 epinephrin solution will temporarily restore consciousness and permit the patient to swallow carbohydrates.

A constant glycosuria, no matter how slight, in a proven diabetic is proof positive that the diabetes has increased in severity. It is of extreme importance to instruct the patient in the details of diet prior to discharge from the hospital. Neither accurate treatment nor proper instruction can be given outside the hospital. The physician should have a working knowledge of the management of the most important emergencies encountered in diabetes, viz., coma, operative cases, diarrhea, and acute infections.—I. B.

Action of insulin on excitability of the vagus (*Action de l'insuline sur l'excitabilité du vague chez la Grenouille*). Popper (M.), *Compt. rend Soc. de biol. (Par.)*, 1924, **91**, 510-512.

Experiments on the frog failed to show any change in the excitability of the vagus due to the action of insulin. The threshold excitability to the induced current was the test.—T. C. B.

On certain problems in the treatment of diabetes mellitus. Rabinowitch (I. M.), *Med. Clin. N. Am. (Phila.)*, 1924, **7**, 1753-1759.

A general review of the modern treatment of diabetes mellitus, with a report of 2 illustrative cases. Cases in which an acute onset of diabetes had occurred as a result of trauma or infection, though progressing even to the stage of coma or actually in coma, may by the use of insulin recover to the previously existing stage of mild diabetes following the elimination of the exciting factor, and subsequently do well without insulin. The well recognized type of chronic diabetes, however, cannot get along without insulin for any length of time. Dietetic treatment based upon the principle of undernutrition has yielded better ultimate results than that calculated upon basal diets. This applies both to those requiring insulin and those who do not. Glycosuria is not a reliable index to the patient's condition; patients presenting no glycosuria

may still possess high blood sugar and polyuria. These patients may even appear very well and actually gain in weight, but are nevertheless exposed to the various complications of diabetes.—I. B.

**Action of insulin on blood phosphorus** (*Action de l'insulin sur le phosphore du sang*). Savino (E.), *Compt. rend. Soc. de biol. (Par.)*, 1924, **91**, 29.

The injection of insulin in sheep is followed by a fall in inorganic phosphorus parallel with the fall in sugar. Injections of glucose do not prevent this fall.—T. C. B.

**Preparation of insulin** (*Preparation de l'insuline*). Wernicke (R.), *Compt. rend. Soc. de biol. (Par.)*, 1924, **91**, 320-321.

A modification of Sordelli's method, shortening the time of filtration by adding 18 per cent of saturated solution of sodium chloride to the alcoholic extract. A pure insulin is obtained. The method is described in full.—T. C. B.

**The treatment of diabetes in ambulatory patients.** Wiener (H. J.) & Marks (H. E.), *Med. Clin. N. Am. (Phila.)*, **8**, 219-232.

A summary of the treatment of non-hospitalized patients, as carried out in the Vanderbilt Clinic. In such cases there is less direct control of diet and other therapeutic measures, greater difficulty in the carrying out of necessary forms of treatment because of economic, domestic and other circumstances in the patient's life, and there is less frequent contact of the patient with medical attendants, thus necessitating a greater margin of qualitative and quantitative dietary safety. Too often the family physician believes that a decrease in glycosuria is an index of satisfactory treatment and of a favorable prognosis. Again, the importance of the maintenance diet is not always sufficiently appreciated. The effect of fat feeding up to the caloric requirement of the body in sparing the destruction of tissue protein for energy must be borne in mind. The work of Newburgh and Marsh, Woodyatt, Shaffer and others has shown that if protein is reduced to the minimum required for nitrogen equilibrium, fat may be given in relatively large quantities without harm. The question as to the most favorable weight level for these patients is not always easily determined. Obesity is to be avoided, and probably a weight slightly below the average for the height, age and sex is desirable. The author takes up the question of dietetic formulae for ambulatory patients in detail. With regard to insulin, the patient or a member of the household is instructed in the method of administration, and the dosage is determined by the tolerance and the total available carbohydrate of the diet prescribed. Haphazard insulin administration is not only useless but dangerous, and it is often advisable to place patients upon a preliminary course of quantitative limitation in diet

without insulin, in order to fix the habit of rigid quantitative observations of food intake. This will also make for a higher degree of co-operation.—I. B.

The tetany of oestrus, pregnancy and lactation. Dragstedt (L. R.), Sudan (A. C.) & Phillips (K.), *Am. J. Physiol. (Balt.)*, 1924, 69, 477-497.

Tetany may develop during oestrus in thyro-parathyroid-ectomized dogs that have been free from tetany for months on a diet of bread, milk, and lactose. The same is true for pregnancy and lactation. The tetany can be controlled by injection of Ring-er's solution, or sodium chloride solution, or by administering calcium lactate.—T. C. B.

Cholin in the blood after parathyroidectomy. Shanks (W. F.), *J. Physiol. (Lond.)*, 1924, 58, 466-469.

The serum of dogs and cats contain a larger amount of cholin after parathyroidectomy than before. It is suggested that cholin may be a precursor of guanidin in tetania parathyreopriva.

—T. C. B.

The effect of thyro-parathyroidectomy on the adult sheep. Simpson (S.), *Quart. J. Exper. Physiol. (Lond.)*, 1924, 14, 199-207.

Observations on 6 ewes, 5 experimental and 1 control, lead to the conclusion that herbivora such as the sheep tolerate the loss of thyroid and parathyroids much better and for a longer time than do carnivora. This difference may depend on the character of the intestinal flora.—T. C. B.

The effect of chemical compounds on the production of the tetany syndrome. Swingle (W. W.) & Nicholas (J. S.), *Am. J. Physiol. (Balt.)*, 1924, 69, 455-464.

The symptoms occurring in normal cats after subcutaneous, or intravenous or oral administration of methyl guanidine sulphate or nitrate, trimethylamine, ergot, phosphorus, intestinal content, ammonia, etc., were hardly comparable to the reaction of cats suffering from parathyroid tetany. Methylguanidine showed the most marked reaction of subcutaneous injection, but practically no effect after oral administration. Four thyro-parathyroidectomized cats which showed no symptoms of tetany did not develop tetany after injection of methylguanidine.—T. C. B.

Suggesting thymic involvement in pertussis. Adkins (W. N.) & Landham (J. W.), *Arch. Pediat. (N. Y.)*, 1924, 41, 580-581.

The writers see a similarity between thymus enlargement and pertussis. Lymphocytosis, particularly of the small mononuclears,

appear to be a constant finding in both conditions. The manifestations in each are spasmodic in character and asthenia appears constant in both. A spasmodic cough is constant in pertussis and common in enlarged thymus. In enlarged thymus, crying and breath holding spells, with congestion or cyanosis of the face, head and upper chest, are quite common, and in pertussis a protracted spasm of coughing will bring about this condition. The whoop of pertussis is inspiratory, and the stridor of enlarged thymus is more often inspiratory than expiratory. The cough in pertussis is more often more or less stridulous in character, suggesting pressure on the trachea, as is often the case in enlarged thymus. The authors suggest that the beneficial results obtained from x-ray treatment in pertussis are due to the effect on the thymus, and they advise that the thymus be x-rayed at least once in every case of pertussis.—M. B. G.

**The enlarged thymus gland.** Drea (W. F.), *Radiol.*, 1924, 5, 1923.

An enlarged thymus may be present and produce slight symptoms; these cases are often overlooked unless the roentgen ray is used. The author suggests that anterior-posterior enlargement may be present with little lateral extension. In these the usual roentgen ray film would show no thymic shadow, although the clinical evidence was present. The presence of enlarged paratracheal glands may cause a confusing shadow. However, the glands frequently are enlarged on one side only. Radiation with roentgen ray or gamma rays is beneficial in either case. The effect is more rapid on the thymus than on enlarged paratracheal glands. The author, unless the severity of the case demands more intensive treatment, gives 4 roentgen ray treatments at one or two-week intervals, using 5 milli-ampere, 8-inch spark gap, 10-inch skin target distance, 3 mm. Al. screen, and about two and one-half minutes exposure. The milder treatment is used in the belief that absorption is less rapid, and suppression of function less abrupt, although the latter is unknown. Heavier dose may be safely given, and both front and back of the chest exposed. The thyroid should be protected during the exposure. Films are taken to advantage, as they record the process of involution, which may extend over a considerable period after the last treatment is given.—*Am. J. Dis. Child.*, 28, 371.

**Thymus of newborn and its significance to the obstetrician.** Peterson (R.) & Miller (N. F.), *J. Am. M. Ass. (Chicago)*, 1924, 83, 234-238.

Observations were made on the incidence of thymic hyperplasia, and its significance, in 120 infants consecutively born. In all, 96 mothers were studied with respect to age, glandular dyscrasia, multiparity and antenatal complications. Of the 96 mothers studied, 28 showed antenatal complications of sufficient importance to be considered. In this group of 28, 9, or 32%, had infants with abnormal

hypertrophy of the thymus. Four, or 44% of this number, occurred in infants of mothers having had an acute disease during the antenatal period. Probably the most noteworthy information obtained from this study is the effect of syphilis on thymic hypertrophy. Thus, of the 9 cases of syphilis appearing in both mother and child, only 2 of the infants revealed an abnormally large thymus. Hence it can scarcely be said, from this evidence, that syphilis materially increases the tendency to thymic hypertrophy. The incidence of thymic hyperplasia was greater in those cases in which the mother suffered from some acute respiratory infection, than when the infection was localized, as in pyelitis and gingivitis. There was marked increase in the percentage of cases of thymic hypertrophy that were encountered in infants, with the increase in the age of the mothers. Only 34% of primiparas had infants with enlarged thymus glands, while 66% of multiparas had infants with this condition. Of 102 mothers studied for evidence of glandular disturbance, not one revealed any discernible glandular pathologic condition other than simple hypertrophy of the thyroid. Thirty-seven, or 36%, revealed a visible and, of course, palpable thyroid. None showed any positive evidence of hyperthyroidism. Eighteen of the infants from this group of 37 mothers, or 48%, showed abnormally large thymus glands. Of the 120 infants studied, 52, or 43.3%, showed an abnormal enlargement of the thymus. Necropsy reports reveal the interesting fact that status lymphaticus is six times more common in males than in females. Satisfactory explanation of this seems doubtful, other than to classify it with the group of sex predilection diseases. The general impression gained from a study of the infants was that there existed a slight difference in the size of the chest in those with and those without thymic hyperplasia. Thirteen of the 120 infants were born between the eighth and ninth months, and one between the seventh and eighth months. Only 5 of the 14 premature infants, or 35%, revealed thymic hyperplasia. Forty-seven of the 105 term infants, or 44%, showed the same. In many infants, the enlarged thymus glands run an entirely symptomless course. Some infants show symptoms later in infancy or in childhood. In none of the 120 cases were any symptoms attributable to the thymus noted after the second day of life. Not one of the 52 infants with thymic hypertrophy revealed stridor, attacks of suffocation or convulsions after being treated, at least not during their stay in the clinic, which was approximately 6 weeks for the illegitimate, and 2 weeks for the legitimate infants. Twenty of the infants studied, however, showed some symptoms during the first 2 days. Five deaths occurred in the interval from birth to the seventeenth day. The mortality rate was 4.1%. Three babies died of pneumonia, one from acute encephalitis, and one from congenital heart disease and prematurity. None of the deaths was attributed directly to the thymus. A comparison of the mortality rate in the foregoing series with the death rate in a

similar but untreated series of 120 consecutive infants was made. In the series of untreated cases, there were 7 deaths, or a mortality of 5.8%.—Courtesy A. M. A.

**Studies on the physiology of reproduction in birds. XIX. A hitherto unknown function of the thymus.** Riddle (O.), *Am. J. Physiol. (Balt.)*, 1924, **68**, 557-580.

There is, apparently, in the thymus a substance which has a specific action on the oviduct of birds, indispensable to the production of normal egg-envelopes, and to which the name thymovidin is given. It is in the nature of a true hormone.—T. C. B.

**Effect of thyroxin upon the blood sugar of normal and thyroidectomized sheep.** Bodanski (A.), *Am. J. Physiol. (Balt.)*, 1924, **69**, 498-509.

A single dose of thyroxin subcutaneously raised the blood sugar in sheep temporarily. Larger increases were observed when thyroxin was administered every other day. In thyroidectomized sheep the blood sugar was raised only during the first weeks of treatment when the diet was adequate. The mean "fasting" blood sugar was raised in normal sheep, but not affected in cretins.—T. C. B.

**The preliminary thyroid operations.** Bonn (H. K.), *Calif. & Western Med. (San Fran.)*, 1924, **22**, 365-368.

Bonn believes that the surgeon is justified in removing too much of the hypersecreting thyroid rather than not enough, since if too much remains failure to cure results, and if too little, the remainder will hypertrophy until a physiological balance is reached. Preliminary ligations are necessary in those patients who are poor risks; moreover, the resulting reaction is an index to the possible margin of safety for a subsequent thyroidectomy. If one polar ligation fails to put the patient in fit condition for thyroidectomy, another ligation of the superior or inferior thyroid artery may be added. If the patient is unfit for ligation, boiling water injections, as advocated by Porter, may be attempted. The technique of the various preliminary thyroid operations is discussed.—I. B.

**The effect of thyroid extract and of thyroxin upon the response to adrenalin.** Dryerre (H.), *Quart. J. Exper. Physiol. (Lond.)*, 1924, **14**, 222-224.

Acute experiments on cats and rabbits give no evidence that the pressor effect of adrenalin is increased by either thyroid extracts or thyroxin.—T. C. B.

**Pathologic changes in the thyroid body in wild animals.** Fox (H.), *Rep. of the Lab. & Mus. of Compar. Pathol. of the Zool. Soc. of Phila.*, 1924, **11**, 22.

Fox calls attention to the fact that the thyroid body of carnivores is relatively greater in weight than in other orders; it shows at autopsy greater variations in size and appearance, and is known to vary more in seasonal and sexual cycles than does the similar body in other dietary groups. "It is noteworthy that the beast with the largest normal thyroid, showing the greatest variability in size under normal conditions, should show the greatest vulnerability." Definite clinical pictures of thyroid disease for wild animals cannot be given. Photographs and photomicrographs of the following cases are given:—adenomatoid hyperplasia of the thyroid, and adenocarcinoma sarcomatodes of the thyroid with metastases to the lung and liver, in two American Gray Wolves (*Canis mexicanus*); nodular adenomatoid hyperplasia with colloid areas in an Eskimo dog (*Canis familiaris*); and adenomatoid hyperplasia of the thyroid with marked venous stasis in a common wolf (*Canis lupus*). Ten excellent illustrations are included.—J. P. S.

A case of juvenile myxedema. Firth (D.), Proc. Roy. Soc. Med. (Lond.), 1924, 17, 40 (Clin. Sect.).

The patient reported is a female aged 14 who has been suffering since the age of 6 with signs of hypothyroidism, while presenting evidences of infantilism of the Brissaud type. According to the author the administration of thyroid extract gave rise to headache, diarrhea, and vomiting.—I. B.

Heart failure of the congestive type caused by hyperthyroidism.

Hamilton (B. E.), J. Am. M. Ass. (Chicago), 1924, 83, 405-407.

From study of actual cases, Hamilton finds that hyperthyroidism tends to spare the hearts of 65% of even the severely toxic patients. Even when these patients (the 65%) are driven to death by the disease, they do not show truly significant heart changes. But a fraction which is increasingly great in each advancing age decade shows definite heart changes not accounted for by age and coincident disease alone. The first significant heart change is auricular fibrillation. This tends to appear first in transient attacks, hours or days in duration. If hyperthyroidism continues unchecked, the auricular fibrillation tends to become established. If the hyperthyroidism is relieved during the stage of transient attacks of auricular fibrillation, the attacks permanently cease in nearly every case. Fifty patients with signs of true congestive heart failure due to hyperthyroidism were seen by Hamilton among a total of about 900 patients with thyroid disease suffering with some degree of toxicity, all of whom were treated surgically. The histories of these 50 cases, with a very few exceptions, show a predominance of symptoms referable to the heart from early in the course of their disease. The author feels that the universally accepted and great value of elevated basal metabolism readings in the diagnosis of thyroid toxicity has



perhaps led to too great clinical trust in this test alone. The basal metabolism tests in this group of cases with congestive heart failure, taken the day before operation, when the patients had reached maximum improvement under rest and medical treatment directed toward the heart, were as follows: the lowest, plus 16; the highest, plus 125, and the average of the whole group, plus 61.8. More than half the cases gave readings below this average. The test actually proves of only suggestive value in this situation. The typical case of heart failure caused by hyperthyroidism would then be a woman close to 50 years of age, emaciated, weighing, in spite of edema, around 105 pounds (47.6 kg.). She would be deeply pigmented, have no enlargement of the thyroid gland, and no clear exophthalmos. She would be noticeably apathetic, willing to lie quietly for days bolstered up on pillows, saying little, responding slowly and briefly to questions. She would have a markedly enlarged heart without diastolic murmurs or other evidence of rheumatic or syphilitic infection. She would have established auricular fibrillation. In spite of rest and thorough digitalization, her heart rate could not be kept below 100. She would give a history of a surprisingly long duration of complete disability associated with gross signs of heart failure. She might also give a history of a previous attack with relief of symptoms. From this group of 50 cases it appears that auricular fibrillation, transient or established, must be present. Emaciation or a history of marked loss of weight must be present. Pigmentation should be present. Nearly all cases are in women over 35 years of age. Goiter and exophthalmos, though valuable if found, are not commonly present in this group of cases. Persistent elevation of heart rate in spite of rest and digitalization is a valuable sign, but a slow heart rate does not exclude hyperthyroidism. Persistent congestive failure in spite of medical treatment directed to the heart is to be expected in these cases. The response to treatment in this group serves as a final confirmation of the diagnosis, and is unique in experience with persistent congestive heart failure from all causes, as commonly seen. All the patients were given medical treatment directed to the heart condition; namely, the most complete rest (and this includes, where needed, continuous special nursing, isolation, sedatives) and thorough digitalization. Though all the patients improved, at any rate temporarily, to some degree, only 11 of them lost all gross signs of true heart failure. Thirty-nine patients showed persistent demonstrable enlargement of the liver and orthopnea; most of them also had engorgement of the neck veins and râles in the chest.—Courtesy A. M. A.

**Correlation between thyroid weight and body weight.** Hammett (F. S.), *Am. J. Physiol. (Balt.)*, 1924, 69, 510-517.

A statistical study, on rats 150 days of age. Body weight is negatively correlated with thyroid weight when the thyroids above

the mean value for the group are compared with their respective body weights. Body weight is positively correlated with thyroid weight when the thyroids below the mean value for the group are compared with their respective body weights. There is no sex difference.—T. C. B.

**Radiation therapy of the thyroid and ductless glands.** Holmes (G. W.), Boston M. & S. J., 1924, 191, 10-12.

This is a brief statement with case reports. "Radiation therapy is justified in all cases of enlarged thymus in which diagnosis is definitely established. It is also a valuable adjunct to surgery in the treatment of hyperthyroidism." A 12-inch target skin distance and a wave length of 0.28 E. U. are used. "The amount given at each exposure should not exceed two-thirds of an erythema dose and should not be repeated within three weeks." Five or six treatments are usually sufficient. The number should never exceed seven.—J. C. D.

**On the treatment of exophthalmic goiter.** Holmes (G. W.), Means (J. H.), Porter (C. A.), Richardson (E. P.), & Starr (M. P.), Boston M. & S. J., 1924, 191, 295-298.

As the result of 10 years' work the authors conclude that subtotal thyroidectomy is the only cure. The use of iodine in the form of Lugol's solution is recommended as a pre-operative measure, as it brings the patient's basal metabolism down toward normal. This is a temporary result, however, and must be followed by operation. X-ray has the same effect as Lugol's solution in certain cases, but is not so reliable. Charts showing the basal metabolism curves resulting from different treatments are given.

—J. C. D.

**Individual treatment of goiter.** Kaspar (F.), Wien. klin. Wchnschr., 1924, 37, 713-717.

Kaspar had excellent results in treatment of parenchymatous goiters, especially in children, with extremely small amounts of potassium iodid. Doses of 1 to 4 mg. per month, divided in daily doses, were sufficient. These amounts are too small to produce thyrotoxic symptoms.—J. Am. M. Ass., 83, 653.

**Hypothyroidism.** King (J. T.), South. M. J. (Birmingham), 1924, 17, 662-667.

An analysis of 200 consecutive determinations of the basal metabolism at the Johns Hopkins Hospital showed 36 instances of basal metabolism less than minus 10%. Most of these patients are believed to have suffered from thyroid insufficiency, while in a few the cause of the depressed basal metabolism is not clear.

Determination of the basal metabolism is of even more diagnostic aid in cases of hypofunction of the thyroid than in hyperthyroidism, particularly because of the contradictory pulse findings in hypothyroidism and because the clinical manifestations in general are not so clearly defined as they are in hyperthyroidism. Hypothyroidism is much more common in women than in men, and one-half the cases in this series occurred between the ages of 40 and 60. In protracted menopause symptoms, hypothyroidism should be suspected. Cases of chronic eczema and ichthyosis complicated by hypothyroidism are included.

It is believed that the differentiation of cases of hypothyroidism into "primary" and "secondary" is justified. In many of the "secondary" cases, however, the condition responsible for depression of the basal metabolism is probably not thyroid deficiency alone. Treatment by mouth with thyroid extract or thyroxin or subcutaneously with thyroxin should be begun with great caution and continued gradually over months until the basal metabolism is within normal limits. If untoward symptoms develop the dose should be temporarily reduced. Cases of non-absorption of thyroid extract and thyroxin are mentioned.—J. C. D.

#### The metabolism pulse ratio in exophthalmic goiter and in leukemia.

Minot (G. R.) & Means (J. H.), Arch. Int. Med. (Chicago), 1924, 33, 576-580.

In an attempt to answer the question as to the cause of the rapid pulse in hyperthyroidism the authors, for purposes of comparison, plotted the basal metabolic rate (ordinates) against the basal pulse rate (abscissae) for 180 observations in exophthalmic goiter and 110 observations of chronic leukemia (afebrile). They found a high degree of correlation between the data for basal pulse and basal metabolism in both diseases, the correlation coefficient of the curve obtained in exophthalmic goiter being  $0.525 \times 0.036$ , and in leukemia  $0.544 \times 0.044$ , and the ratios in the two diseases were essentially the same. They therefore conclude that the amount of pulse elevation for a given metabolic rate elevation is essentially the same in hyperthyroidism and in chronic leukemia. From this it is inferred that in both diseases the tachycardia is chiefly the result of an increased metabolic rate. Certain symptoms of hyperthyroidism which are believed to be the expression of an increased metabolic rate also occur in leukemia likewise invariably characterized by increased H. L.

1 cretinism. Pfaundler (M.), Jahrb. f. Kinderh. 1905, 223.

11el between the content of radioactive sub-  
lemic goiter. The known facts support

the theory that such substances are an important etiologic factor, but are insufficient either to prove or disprove it. There is a close correlation between endemic goiter and cretinism, not only in the same person but between mother (goiter) and child (cretinism). In addition to the external factors there are internal factors. There is the true hereditary factor in which goiter and cretinism act as simple recessives, and also the inability of the mother during pregnancy to furnish proper protection to the developing anlagen.—Am. J. Dis. Child, 28, 372.

**Death from iodine hyperthyroidism.** Roth (O.), *Deutsches Arch. f. klin. Med.* (Leipz.), 1924, 144, 177-188.

Roth reports the history and necropsy findings on a girl, aged 21, who had received 9 gm. potassium iodid within 4 weeks in treatment of colloid goiter. The patient developed symptoms of toxic goiter within 14 days after the beginning of the treatment, and died two and one-half months later. A thymicolymphatic state and hypoplasia of the heart and blood vessels acted perhaps as a predisposing cause.—J. Am. M. Ass., 83, 649.

**Effects of thyroidectomy on the cutaneous system in the sheep and goat.** Simpson (S.), *Quart. J. Exper. Physiol.* (Lond.), 1924, 14, 185-197.

Thyroidectomy in sheep causes, in certain cases, a falling out of the wool, and in all cases a diminution in the weight of the fleece. In sheep and goats the rate of horn growth is retarded.—T. C. B.

**Growth of untreated mongolian idiots.** Talbot (F. B.), *Am. J. Dis. Child.* (Chicago), 1924, 28, 152-158.

There are several factors of growth in common between the cretin and the mongolian idiot. The arms, legs and feet in both conditions tend to be shorter than normal, more so in the former than in the latter. The greatest differences in their physical measurements is noted in the circumference; that of the mongolian idiot is less than normal while that of the cretin falls within normal limits. The author has prepared charts which show the expected physical development of untreated mongolian idiots and which may be used for comparison in measuring the effect of treatment on the physical development.—M. B. G.

**The electrocardiogram in cretinism and in mongolian idiocy.** Thacher (C.), *Am. J. Dis. Child.* (Chicago), 1924, 28, 25-28.

From a study of 8 cretins and 12 mongolian idiots, it appears that in pure cretinism as in myxedema in adults the T-wave in the electrocardiogram is lowered, flattened or even inverted, and can be brought up to normal by the administration of thyroid. In mongolian idiocy there is no characteristic change in the electrocardiogram.—M. B. G.

**Iodin treatment of hyperthyroidism.** Wahlberg (J.), Finska läk.-sällsk. Handl. (Helsingfors), 1924, 66, 385-398.

Wahlberg's treatment differs from the usual technic in that he uses only minute doses, never more than 0.04 gm. of potassium iodid. He gave at most 15 drops a day of a 1:20 solution, and all his 9 patients thus treated materially improved and 5 can be regarded as cured. In the others, the improvement was transient, and in some the condition was graver at the close of treatment than before. He ascribes this to cumulative action from too long continuance of the optimal dose.—J. Am. M. Ass., 83, 654:

**The structure of the thyroid gland in man.** Williamson (G. S.) & Pearse (I. H.), J. Path. & Bacteriol. (Edinb.), 1923, 26, 459-469.

This exceptionally well illustrated article sets forth a view of the structure of the human thyroid that is radically different from that usually described in textbooks. The authors are convinced that the vesicle of the literature forms no part of the functional unit of the thyroid. Concisely stated, the authors' view is that "the functional gland-unit of the thyroid organ is essentially a lymphatic sinusoid in which float columns of epithelium enmeshed in a highly specialized plexus of blood capillaries." The secretion of the thyroid organ is produced and stored in a specific fashion; it is not the same as colloid. The authors set forth the sequence of the process of secretion in the thyroid as follows: "(1) the opening up of the potential space of the lymphatic sinusoid by fluid matter; (2) a change in the endothelial cells lining the sinusoid associated with which lymphocytes appear in the intralobular lymph channels, and frequently also in the sinusoidal spaces; (3) swelling of the epithelium, migration of the nuclei to the extreme periphery and the appearance of two orders of granules; (4) vacuolation of the protoplasm and partial solution of the granular matter in the fluid of the vacuoles; (5) lacunation of the epithelium by the accumulation of the contents of the vacuoles in the central core of the column of epithelium; (6) the tubules in the protoplasm of the epithelium appear to swell and conduct granular fluid, the radial branches become turgid." The authors believe that colloid matter is stored in another manner; and that it is possibly a vehicle for the carriage of some metabolite.

—J. P. S.

**The effects of thyroid and some other endocrine products on paramcium.** Woodruff (L. L.) & Swingle (W. W.), Am. J. Physiol. (Balt.), 1924, 69, 21-34.

Using thyroxin to eliminate the food factor in thyroid feeding, it is found that there is no acceleration of cell division in paramcium, and if the concentration of thyroxin is high there is a depression of cell division.—T. C. B.

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